**TAMPERE UNIVERSITY, Faculty of Medicine & Health Technology**

# CELLULAR PROCESSES AND SIGNALS

# BTK4332

# FINAL EXAMINATION 2020

**Time: 3 Hours**

Thursday 20 February, 16:00-19:00

- *Answer all questions in Section A, all questions in Section B and the one question in Section C*
- *Each section carries one-third of the total marks*
- *In Section A all 10 questions carry equal marks. In questions with multiple choice format, the number of correct answers is as indicated, or is left open. Read each question carefully.*
- *In Section B all questions carry equal marks.*

*Use clear diagrams to illustrate your answers, where appropriate.*

## SECTION A

Answer all questions. All 10 questions carry equal marks. One word or a short phrase is sufficient for all answers.

1. In a classic paper, Wilson (1892) reported a mosaic pattern of development in the embryo of the marine annelid worm *Nereis lumbata. Nereis* embryos exhibit a 'spiral' pattern of stereotypic, unequal cleavage, shared amongst all molluscs, annelids and many other invertebrates. Recent studies have shown that the differently fated blastomeres of these spiralian embryos inherit a subtly different population of RNA molecules, of which over 90% are common to all blastomeres, but 3-4% are unique.

(i) Define mosaic development.

(ii) Suggest what class of proteins the 3-4% of blastomere-specific RNAs might code for.

2. The subunit of a trimeric G-protein that interacts directly with a GPCR is:

(a) the α subunit
(b) the regulatory subunit of PKA
(c) a GEF
(d) a GAP

3. The N-terminal half of the helical PilA protein of *E. coli* has weak similarity (~10% identity) with proteins from many different archaea and some eukaryotes, whilst the entire protein has very strong (~95%) identity with sequences reported as coming from several insect species. Further study has found the insect sequence in question to be 100% identical to an open reading-frame predicted from the genome of *Enterobacter cancerogenus*, an opportunistic bacterial pathogen found occasionally in humans and also in excrement from the larvae of some wood-boring insects.

(i) What is the function of the PilA protein in *E. coli*?

(ii) What is the function of the weak homologues found throughout the archaea?

(iii) Which of the following explanations do you find plausible to explain the finding of a very similar protein in just a few species of insect, as well as in *E. cancerogenus*?

(A) the insects in question have by chance evolved a protein of very similar structure to bacterial PilA, but of unknown function
(B) the common ancestor of the insects in question must have acquired the PilA gene from a bacterial species, via horizontal gene transfer
(C) the DNA preps from those particular insects were contaminated by bacterial DNA from the environment, and the above finding is a pure artefact
(D) the insects in question must harbour *E. cancerogenus* or a very similar species in their gut microbiota
(E) the PilA gene of *E. coli* was acquired by horizontal transfer from the DNA of a woody tree species

(iv) What biological advantage does this gene confer on *E. cancerogenus*?

4. Which protein kinase phophorylates eIF2 when stimulated to do so by dsRNA?

5. Pair the following proteins or protein families with the appropriate process in immune cell extravasation:

Protein families: (a) TNFα / (b) integrins / (c) selectins / (d) PECAM

Processes: (i) tight adhesion / (ii) chemoattraction / (iii) transmigration / (iv) rolling adhesion

6. (i) What happens to eIF2B during heat-shock?

   (ii) Is eIF2B a translation initiation factor, a GAP, a GEF, a serine/threonine kinase or a combination of all of these?

   (iii) Which subunit of eIF2 binds GTP?

7. In a clinical study of a mitochondrial disease, characterized by various neurological phenotypes including a form of epilepsy, a drug (XVC), commonly used to treat epilepsy, was found to produce irreversible liver failure in more than a dozen patients. iPS cells derived from one of the patients were differentiated *in vitro* into hepatocytes and tested with various doses of XVC, in comparison with control iPS-derived hepatocytes. The patient-derived cells became growth-arrested and eventually died by apoptosis at doses of the drug1000 times lower than the control cells.

   Which ONE of the following statements would you consider most appropriate, in the light of these findings.

   (a) mitochondrial disease patients treated with XVC should be treated with potent anti-apoptotic drugs at the same time

   (b) mitochondrial disease patients could be treated with hepatocytes derived from their own iPS cells, but only after those hepatocytes have been grown for many generations in cell culture in the lab, under selection for resistance to XVC

   (c) mitochondrial disease patients suffering from epileptic seizures should not be treated with XVC

   (d) mitochondrial disease patients suffering from epileptic seizures can be safely treated with XVC, but only at doses 1000 times lower than used for other patients

8. Which of the following statements about the heat-shock transcription factor Hsf1 in yeast is (or are) correct:
   (a) Active Hsf1 adopts a homotrimeric structure
   (b) Hsf1 has over 100 transcriptional targets in the yeast genome.
   (c) Hsf1 always acts as a transcriptional activator
   (d) The first step in the activation of Hsf1 is an unorthodox splicing event in its cytosolically located mRNA

9. The non-receptor tyrosine kinase c-Src has a number of functional regions, most importantly a catalytic domain centred on tyrosine 416, an inhibitory C-terminal tail region, and some specific structural elements (SH2 and SH3 domains) found in many other proteins. c-Src is positively regulated by dimerization, which involves interactions between the myristoylated N-terminal region of one partner and the kinase domain of the second. Dimerization activates the enzyme via autophosphorylation of Y416. c-Src is negatively regulated by phosphorylation at tyrosine 527, in the inhibitory tail. The activation of c-Src causes the dephosphorylation of Y527. This induces long-range conformational changes within the protein, resulting in the opening up of the SH3, SH2 and kinase domains, allowing the autophosphorylation of Y416.

   Suggest mutations of the c-Src-encoding gene that could result in the following outcomes:

   (i) Constitutive activation of c-Src
   (ii) Constitutive inactivation of c-Src

10. Which of the following statements about CDKs is (or are) correct?
    (a) CDKs are inhibited by their partner proteins, the cyclins
    (b) CDK1 (Cdc2 in *S. pombe*) is phosphorylated by Wee1, which inactivates it
    (c) Cdc2 reinforces its own activation by a positive feedback loop in which it phosphorylates both Wee1 and Cdc25
    (d) A single CDK controls all phases of the cell cycle

**END OF SECTION A**

## SECTION B

Answer each question. A maximum of 200 words (and/or clear diagrams) is sufficient to answer each question.

11. Regarding the major classes of cell-surface receptors in animals: are there more or fewer of these receptors in plants, and why?

12. Why is cytosolic translation an important target of the mitochondrial UPR?

13. Cardiomyocytes are highly dependent on mitochondrial energy, and also require continuous waves of $Ca^{2+}$ release to synchronize contractions across the myocardium. Yet mitochondria are vulnerable to calcium overload, which can cripple mitochondrial function by opening pores in the inner membrane that abolish membrane potential. If prolonged, this is irreversible and fatal for the cell as well as the organelle. How can such an essential organ have evolved, so as to be so endangered by the very thing that keeps it going?

14. Does apoptosis occur in plants?

15. How could inteins be used to introduce into mammalian cells a large protein whose coding sequence is too long to fit into a conventional expression or gene therapy vector?

16. The Rag genes, which catalyze the recombination steps that enable the somatic rearrangement of immunoglobulin and T-cell receptor genes, are the cornerstone of adaptive immunity in vertebrates. But once such a system had evolved, why didn't it become operative in many other developmental processes, keeping the genome constant only in the germline?

17. Some viruses drive the cell cycle, but others arrest it. What advantages are there for the virus in adopting either of these strategies?

18. Could sea urchins have adaptive immunity?

19. Cancer cells produce extracellular vesicles (EVs or exosomes) that have been proposed to deliver functionally important signals to surrounding non-neoplastic cells, favouring tumour growth. Are there any examples of 'normal' cells using this as a physiological means of cell-cell communication? How could EVs achieve programmed target-cell specificity?

## END OF SECTION B

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## SECTION C

20. During this course, you have studied TWO review papers in detail, relating to different aspects of molecular cell biology. Write 'public-access' summaries of EACH of them, aimed at a class of high-school students with no specialist knowledge of biology, explaining the importance of the topic and what has been found out about it (max. 1 page for each paper that you studied).