

Mutations, Proteins, and Disease

Scientific Foundations

Readiness Assessment Questions

1. In a patient with pre-diabetes, serum glucose concentrations can remain high for several hours. Which pathway would be activated in pancreatic β -cells during this period?
 - A. Apoptosis
 - B. Necrosis
 - C. Unfolded protein response
 - D. Protein glycosylation

2. You are volunteering in a clinic that is treating people who are fleeing a forest fire. Many show signs of respiratory problems, and biopsies reveal an increase in cell death in the respiratory tract. Later, you identify a compound in smoke that inhibits the activity of HSP70. What was most likely causing cell death in the respiratory tracts of the patients in the clinic?
- A. Accumulation of protein stuck in secondary structure
 - B. Accumulation of protein with increased activity
 - C. Accumulation of protein mislocalized in the cell
 - D. Accumulation of protein with a longer half-life

3. Insulin resistance is caused by a decrease responsiveness of skeletal muscle cells to insulin. Which change to the insulin receptor might indicate insulin resistance?

- A. Increased expression
- B. Increased ubiquitylation
- C. Increased affinity for insulin
- D. Increased binding to HSP90

4. Fanconi anemia is a genetic disease that predisposed patients to cancer. The mutations cluster in a gene that encodes a protein involved in DNA repair. Mutations differ in how severely they alter the activity of the protein, with more severe mutations leading to higher rates of cancer. Proteins with mild mutations would likely associate with which protein?

A. Proteasome

B. E3 ligase

C. HSP70

D. HSP90

Application Questions

Question 1

You are working with patients who have been diagnosed with pancreatic cancer. An experimental drug slows the growth of pancreatic tumors by inhibiting Akt. Akt is a kinase that stimulates cell division when active. Over time, however, the effect of the drug wanes and the tumors start regrowing. You sequence the AKT gene in patients whose tumors are resistant to the drug and find a novel mutation in the coding region. To test the activity of Akt with the novel mutation, you express the mutated version of AKT in bacteria and purify it. You find the activity of the mutated AKT is much lower than normal AKT.

1. Why the drug loses its efficacy?
2. Why does the mutated AKT have lower activity compared to normal AKT when purified from bacteria?
3. Do the results suggest a potential treatment for patients with drug-resistant tumors?

Question 2

A 24 year-old complains about frequently tripping while walking. The patient's history reveals three years of occasional numbness in their feet. The patient also reports suffering numerous sprained ankles as a child. A physical exam uncovers muscle weakness in the lower limbs.

A nerve conduction test measures a 30 m/s in the patient's nerve (normal is 50 m/s to 60 m/s)

Based on the outcome of the what would your initial diagnosis be?

Sequencing does not identify a mutation or deletion in a gene associated with a disease of the peripheral nervous system or skeletal muscle. However, sequencing does uncover a duplication of a segment of the patient genome that includes PMP22. Your research reveals that PMP22 is expressed in Schwann cells and encodes a transmembrane protein which localizes to myelin.

Develop an explanation for how a gene duplication of PMP22 leads to the pathology in the patient. How would you approach developing a treatment for the disease?

Question 3

Cystic fibrosis is caused by mutations in the CFTR gene which encodes a chloride transporter. The most severe form of the disease is caused by a deletion of phenylalanine at position 508 ($\Delta 508$). Protein from CFTR $\Delta 508$ is synthesized but most of it does not reach the cell membrane.

You are screening a large library of compounds trying to find those that will improve chloride conductance in cells that express CFTR $\Delta 508$. The graph below shows the results from one compound. How could the compound increase chloride transport?

