Research
Based
Curricula

Mitochondrial Dysfunction and Disease

Key Stage 4

Biology

2020

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Resource One Model Answers

Answers

1. Fill in the blanks:
    a) Nucleus (porous membrane)
    b) Lysosome
    c) Golgi apparatus
    d) Mitochondria
    e) Cell membrane
    f) Ribosome
    g) Endoplasmic reticulum
    h) Cytoplasm
    i) DNA (throughout nucleus)
2. Consider the cell as a city:
    a) Transport system – endoplasmic reticulum, as it moves substances from one part of the cell to another. Or Golgi apparatus as this also distributes substances across the cell.
    b) Power plant – mitochondria, as they produce energy for the whole cell
    c) Border control – plasma membrane or nuclear membrane/envelope, as it controls passage of substances in and out of the cell
    d) Waste disposal – lysosomes, they contain digestive enzymes to remove old or misfunctioning organelles
    e) Army – lysosomes, defend against pathogens that invade the cell

Resource One Model Answers

Answers

3. What is the function of a membrane (cell or organelle)
    - Protect the cell from the outside environment
    - Transfer molecules into/out of the cell/organelle
    - Protect the cell from digestive enzymes such as in the lysosomes
4. Muscle cells have increased amounts of which organelles?
    d) Mitochondria – they contain more mitochondria because they have an increased demand for energy
5. Explain how individual organelles present within a cell contribute to the cell's overall function within a whole organism
    - Organelles keep cells alive, cells build tissues, which form organs, and organs work together to keep the organism alive.
6. Tay Sachs is a congenital disorder in which waste molecules called gangliosides are not properly digested and instead accumulate in cells, causing toxicity. Dysfunction in which organelle can lead to Tay Sachs? Justify your answer. (Use your knowledge of the function of different organelles to decide)
    d) Lysosomes are the organelle responsible for digesting waste material. Therefore a misfunctioning lysosome will not digest waste material, and instead it builds up in cells, and interfere with cell functions.

Resource Two
Model Answers

Answers

1. An amino acid is made up of:
    - An **alpha** carbon
    - Carboxylic group
    - **Amino** group
    - Hydrogen group
    - Side chain (-R)
2. Fill in the blanks:

Amino Acid	**Three Letter Abbreviation**	**Single Letter Abbreviation**
Alanine	Ala	**A**
Arginine	Arg	R
Asparagine	Asn	N
Aspartic Acid	**Asp**	D
Cysteine	**Cys**	C
Glutamine	Gln	**Q**
Glutamic Acid	Glu	E
Glycine	Gly	**G**
Histidine	**His**	H
Isoleucine	Ile	I
Leucine	**Leu**	L
Lysine	**Lys**	K
Methionine	Met	**M**
Phenylalanine	Phe	F
Proline	Pro	P
Serine	Ser	S
Threonine	**Thr**	T
Tryptophan	**Trp**	W
Tryosine	Tyr	**Y**
Valine	Val	V

Resource Two Model Answers

Answers

3. What is the definition of the following terms:
    - Amino acid: **organic compounds** that make up proteins, the building blocks of life
    - Polypeptide chain: a chain of amino acids linked by **peptide bonds**
    - Primary structure: the **sequence** of **amino acids** in a **polypeptide chain**
4. How many amino acids make up one turn in a common alpha helix?
    - 3.6
5. Where are hydrophobic amino acids typically found in the 3D protein structure? Justify your answer.
    - The hydrophobic amino acids lay in the **interior** of the protein because they are **repelled** by the **water** in the environment
6. Explain how changes to a protein structure can lead to human disease. In your answer, consider all levels of protein structure, and the role of proteins in the body.
    - Using haemoglobin in sickle cell anemia as an example (or other correct example).
    - Single mutation to the sequence of amino acids in the primary structure, valine to glutamate on the 6th aamino acid of the sequence
    - The –R groups are different and so leads to changes in the secondary, tertiary (3D structure of individual haemoglobin is affected) and quaternary structures (they clump together).
    - This clumping together results in sickle shaped blood cells that cannot bind oxygen as well
    - This results in the individual experiencing an interruption of blood flow, pain and fatigue.

Resource Three Model Answers

Answers

1. Why does the inner membrane fold up into cristae? Explain why this is important for the function of mitochondria.
    - To increase its surface area
    - This is the site of the electron transport chain; an increased surface area means it can host more ETC proteins and therefore produce more ATP
2. Describe the difference between mitochondrial fission and fusion, and the importance of both.
    1. Fission is used to create new mitochondria; it is important because it removes damaged mitochondria
    2. Fusion is used to mix the contents of partially damaged mitochondria with healthy mitochondria; this is important in controlling cell stress
3. Kearns-Sayre syndrome is a disease caused by deletions in circular DNA that codes for proteins of the electron transport chain. What is the inheritance pattern of this disease? Justify your answer.
    a) Through the maternal line - The electron transport chain is found in mitochondria. Mitochondria have their own DNA. When an egg and sperm come together, the zygote's cytoplasm is maternal in origin. Mitochondrial DNA disorders are transferred through the maternal line, as mitochondria replicate independent of the rest of the cell and are passed from the mother's egg.

Resource Three Model Answers

Answers

4. Explain the role that mitochondria play in the following mechanisms:

    - Protection against viruses: using their antiviral signaling protein (**MAVS**)
    - Homeostasis: maintain **calcium** homeostasis, also their **quality control** systems maintain homeostasis of the cell
    - Apoptosis: induce apoptosis by releasing **cytochrome *c*** in response to cell stresses. This activates **caspase** which is involved in apoptosis. Control of calcium levels. Reactive oxygen species.

5. Define the role of the proton gradient within the electron transport chain

    - The proton gradient is where there is a higher concentration of protons outside the inner membrane than in the matrix, this helps **drive ATP production**

Resource Four Model Answers

Answers

1. Define the following terms:

- Communicable disease: caused by **pathogens**, and **transferred from one organism to another**
- Risk factor: something that increases your **risk** of having a certain disease
- Immune deficiency: a disorder that arises when the host's **immune system fails to prevent infection**
- Biotic agent: a **living** organism
- Hyperplasia: areas of **increased cell growth** in tissues or organs
- Etiological classification is when you separate diseases by **cause**

2. Link the following diseases to the most appropriate origin:

Schizophrenia	→	Psychiatric
Malnutrition	→	Nutritional
Hyperthyroidism (excess of thyroid hormone)	→	Endocrine
Cancer	→	Growth of abnormal cells
Coronavirus	→	Biotic agent
Hay fever	→	Immune
Frostbite	→	Physical injury
Sickle cell anaemia	→	Genetic

Resource Four Model Answers

Answers

3. If you knew that there was a high rate of cardiovascular disease within your family, what changes you could make to reduce your own risk of cardiovascular disease?
    - Don't smoke
    - Eat healthily
    - Maintain healthy cholesterol levels
    - Reduce stress

4. Many diseases have a huge impact globally, some examples include HIV, malaria and cholera. Malaria affects over 200 million people worldwide, particularly in developing countries.
    d) Is malaria an example of a communicable or non-communicable disease?
        - communicable
    e) What parasite causes malaria?
        - mosquito
    f) Suggest why diseases such as malaria is more prevalent in developing countries?
        - Less access to health services
        - Sanitation levels are lower

Resource Four Model Answers

Answers

5. Describe the process of evolution of antibiotic resistance in bacteria.
    - In every population there is genetic variation, so some bacteria are resistant whilst others aren't.
    - When bacteria encounter an antibiotic, some are killed or prevented from growing.
    - The individuals that survive will have a higher proportion of individuals with the resistant gene.
    - The next generation will contain more bacteria with the resistant gene.
    - The next time that the bacteria are exposed to the antibiotic the process is repeated.
    - With prolonged exposure to the antibiotic, the population of bacteria will eventually only contain individuals with the resistant gene.
    - This particular antibiotic will then be ineffective against this strain of bacteria.
    - People infected with the bacteria will not respond to drug treatment using this antibiotic
6. Discuss the difference between risk and cause. In your answer give examples of both.
    - Risk: something that increases the likelihood of an individual developing a certain disease. Smoking can increase the risk of cancer. Stopping smoking prevents cancer, but it does not cure cancer.
    - Cause: the aetiology of an illness, what causes the disease to develop. A mutation can cause a disease.
    - A risk factor might eventually lead to an illness, but then it is no longer a risk factor, it is then the cause.

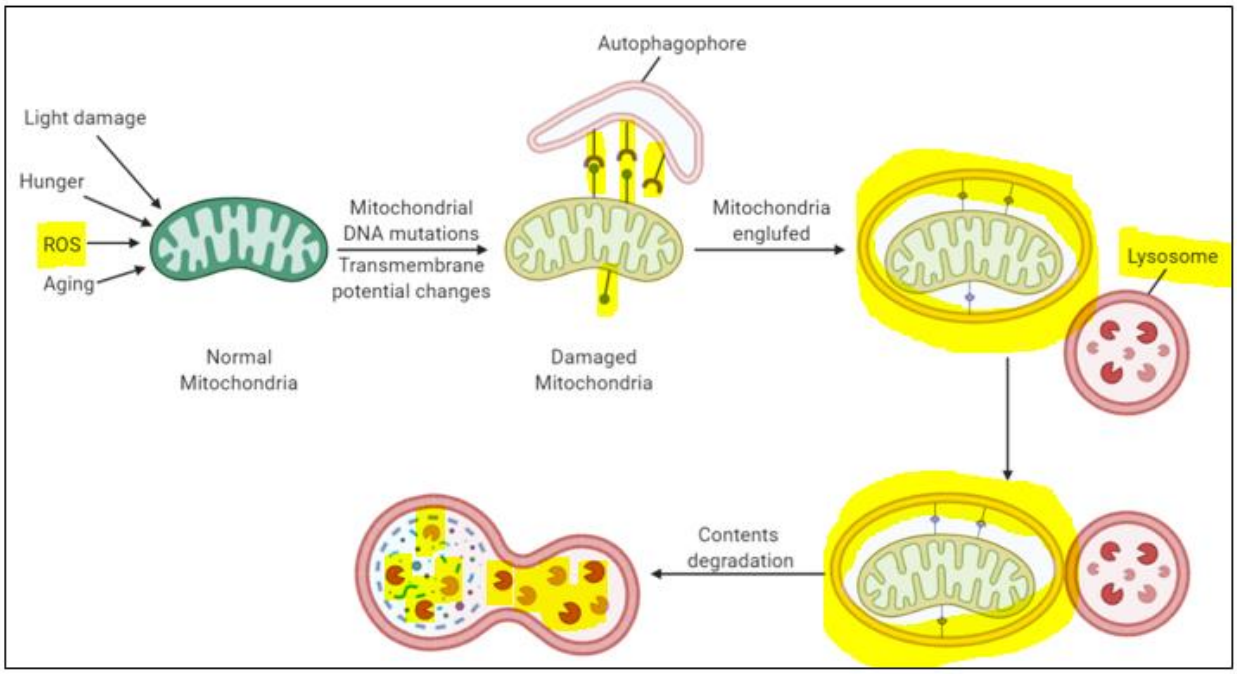
Resource Five Model Answers

Answers

1. Why is mitochondrial DNA more susceptible to DNA damage than nuclear DNA?

    - Because it is positioned close to the **toxic free radicals** produced by the electron transport chain

2. Draw in the missing features and labels of the process of mitophagy below: (highlighted)



3. If mitochondria are the problem in so many diseases, why can't we just destroy all cells with faulty mitochondria?

    - Faulty mitochondria are found in most cells, this is just a process of life, targeting this would lead to massive cell loss

Resource Five Model Answers

Answers

4. How many mitochondria are found in a cell?
    - Varies between cells, depends on the requirements of the cell, but typically 2,000+

5. Discuss how mutations to mitochondrial DNA can present as diseases with such varying symptoms.
    - Consider the different roles that mitochondria have within the cell
        - apoptosis, viral infection, calcium homeostasis, energy production etc
    - Reflect on the different roles that mitochondria have within an individual
        - Immune response, energy production for muscles etc
    - Discuss how dysfunction of these roles might cause the different symptoms and an overall disease
        - Mitochondria are found all over the body in lots of cell types, the symptoms can also depend on the cell type (e.g. brain cells vs muscle cells)
        - Damage to mtDNA can cause more damage to mtDNA, more mutations
        - Diseases with mitochondrial dysfunction are multisystem disorders that affect more than one type of cell, tissue or organ

Resource Six Model Answers

Answers

1. In terms of disease therapy, explain why it is important to keep biodiversity in plants?
    - Because a large number of disease therapies have come from plants. Losing biodiversity could mean potentially losing therapies that have not yet been discovered.
2. Sort the following stages of clinical testing into the correct order, and describe briefly why this stage is done:
    1. Computer modelling of drug interaction (efficacy)
    2. Testing the drugs in human cells grow in the lab (potentially side effects)
    3. Animal testing (side effects)
    4. Testing on healthy volunteers (safety/toxicity)
    5. A small number of people with the illness – low dose (safety and efficacy)
    6. A small number of people with the illness – optimum dose (to determine the optimum dose)
    7. Long-term human trial (to ensure efficacy over long-term and that it doesn't cause side effects)
3. Discuss the advantages and disadvantages of studying a disease on a human cell line, such as HeLa cells?
    - Pros:
        - Adaptable
        - Saves time and money
        - Reproducible
        - ethical
    - Cons:
        - Not a real human and the results *in vitro* are not always the same as *in vivo*

Resource Six Model Answers

Answers

4. Define the following terms:
    - Bias: cause to feel or show prejudice against someone or something
    - Open-label trial: everyone knows what group the patient is in
    - Dosage: how much of the drug an individual needs to take
    - Placebo: something that looks exactly like the new medicine but has no active ingredient in it. A control.
    - Placebo effect: when the individual taking the placebo thinks they are
5. Consider why it takes approximately 12-15 years to approve a new drug.
    - Because the testing process is extremely rigorous and long. Many drugs fail. The process is also expensive.
6. Discuss why is it so important to ensure proper testing has been performed on a drug before it goes to market.
    - To ensure something like thalidomide doesn't happen again
7. Would it be better to discover a whole new drug or re-purpose an already used drug for a different disease? Justify your answer.
    - Re-purposing an old drug means you do not have to go through the lengthy research process and waste time and money
    - However, depending on how old the drug is, it may not have been through the same rigorous testing that is required today, so you may have to repeat those steps

Resource Six Model Answers

Answers

8. Contemplate the considerations that a researcher must have before choosing a disease model to study the effects their potential drug has on a particular disease.
    - Is it appropriate for the disease?
    - How similar is it to humans?
    - Does it have the gene/protein I am studying?

Final Reflection Activity Further Guidance

Deep Dive

Below is an example answer to the final reflection activity using the information available in the resources:

Title

Role of Protein X in Mitochondrial Dysfunction and how it can be Targeted for Parkinson's Disease Therapy Using Drug Y

Introduction

Parkinson's disease is the second most prevalent age-related neurodegenerative disorder in developed societies, with an estimated occurrence of 0.2% of society, and 1% of those over the age of 60 (Poewe 2006). The economic cost of Parkinson's disease is estimated to be nearly $51.9 billion annually worldwide, and with a continuously aging population, this figure is bound to rise (Yang, *et al.* 2020). The development of Parkinson's disease is thought to be due to the degeneration of a region of the brain and depletion of dopamine. Our understanding of Parkinson's disease has advanced in the last few decades, due to the evidence of oxidative stress and mitochondrial involvement. This is starting to shed light on the mechanism of pathogenesis and is beginning to provide new approaches to treatment and prevention of disease.

It is thought that by the time of diagnosis, a Parkinson's disease patient has already lost 30-70% of the dopamine neurons in their substantia nigra region of the brain (Cheng, *et al.* 2010). This is a difficult time to start treatment. The current therapies for neurodegenerative diseases are focused on the management of symptoms and are not capable of slowing, stopping or reversing the continued loss of neurons. To date, no therapy exits to restore mitochondrial function.

Parkinson's disease is characterised by damage to the nervous system, cognitive decline and alterations to brain function and behaviour. Some features of the disease include oxidative damage and mitochondrial dysfunction, which leads to death of neurons. Many of the genes associated with neurodegenerative diseases can be linked to mitochondria. In addition, aggregated misfolded proteins (α-synuclein) are known to inhibit mitochondrial function and induce oxidative stress, resulting in apoptosis. Therefore, the investigation of mitochondrial dysfunction, will increase our understanding of the essential requirements for neuronal survival that can inform future neuroprotective therapies.

With mitochondrial dysfunction and the disruption of normal mitochondrial dynamics acting as underlying features in most diseases, it stands as a potential target for many different fields of therapy research.

Final Reflection Activity Further Guidance

Deep Dive

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Aim & Objectives

The aim of this project is to provide evidence that Drug Y acts on Protein X to prevent mitochondrial dysfunction. This should lead to more effective, disease-modifying treatment for Parkinson's disease.

Objectives:

- Use computational studies and disease models to determine how Drug Y inhibits mitochondrial dysfunction through Protein X
- Alter Drug Y until it is more specific and targeted to Parkinson's disease
- Determine the efficacy of Drug Y in healthy volunteers and patients with Parkinson's disease through a double-blind clinical trial

Study Design and Methods

- Computational studies – modelling protein X with drug Y present
- Alter drug Y to make it more specific for Parkinson's disease instead of liver disease
- Run trials with the different variations of Drug Y to determine the most effective and safe drug
- *In vitro* studies using cell models (appropriate for the disease, e.g. SH-SY5Y cells), determining mechanism of therapy, how well it works and any downstream effects
- *In vivo* studies using an animal model (appropriate for the disease, e.g. mouse treated with MPTP), monitoring for side effects
- Double-blind clinical trial using healthy volunteers to determine if the drugs are safe in humans
- Double-blind clinical trial in a small number of volunteers with Parkinson's and a healthy control group with age-matched volunteers, to confirm it is safe and effective
- Long-term open label human trials to monitor downstream effects and long-term efficacy of the drug. Open label because Parkinson's disease is a relatively debilitating disease off medication so it would not be fair to give patient's the placebo in the long term

Final Reflection Activity Further Guidance

Deep Dive

Issues That May Arise

The drug could fail at many points in the testing process. Because it is a drug that has already been used, it has already been proven to be safe in humans so there is a better chance it will succeed.

References

Poewe, W., *The natural history of Parkinson's disease.* J Neurol, 2006. **253** Suppl 7: p. Vii2-6.

Yang, W., Hamilton, J.L., Kopil, C. *et al.* Current and projected future economic burden of Parkinson's disease in the U.S.. *npj Parkinsons Dis.* **6,** 15 (2020).

Cheng, H.-C., C.M. Ulane, and R.E. Burke, *Clinical progression in Parkinson disease and the neurobiology of axons.* Annals of neurology, 2010. **67**(6): p. 715-725.

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