Ministério da Educação
Universidade Federal de Santa Maria
Centro de Ciências Naturais e Exatas
Programa de Pós-Graduação em Bioquímica Toxicológica
Edital 65/2024 – Processo Seletivo da Pós-graduação – Ingresso 2025

Prova de conhecimentos gerais em Bioquímica e Biologia Molecular

Nível Doutorado

Nome do candidato:

Instruções

- A prova tem duração de duas horas.
- É permitido consultar dicionário Inglês/Português.
- O caderno de questões e a folha de respostas definitiva devem ser entregues aos avaliadores.
- O caderno de questões e o gabarito final serão publicados na página do PPGBTox no dia 11/11/2024.
- Cada questão tem apenas uma alternativa correta.
- Responda as questões conforme o texto.

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The Genotoxicity of Stress

by

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Psychological stress can be described as “a physical or psychological stimulus that can produce mental tension or physiological reactions that may lead to illness”. Significant current stressors include caregiving, social isolation, people’s ability to work, and a lack of community and family support. It is well-known that stressors such as social isolation are prognostic risk factors for increased morbidity and mortality and reduced quality of life. Stress results in the production of stress

response hormones, glucocorticoids (GC) and catecholamines such as epinephrine (E) and norepinephrine (NE), which directly bind to receptors on the surface of most cells activating complex downstream signaling pathways. Cortisol functions by binding to cytosolic glucocorticoid receptors (GR), while E and NE function by binding to β-adrenoceptors (β-AR).

Damage to our DNA can lead to mutations and genomic instability. DNA damage response pathways are important for maintaining a healthy genome, and dysregulation in DNA damage and repair pathways has been closely linked to various diseases including cancer. Stress hormones have been shown to rapidly induce DNA damage transformation, and tumorigenicity in normal fibroblast cells after both short and long-term exposure, with inhibition of the GR and β-AR negating the effects [1]. In both human and animal studies, increases in negative psychosocial factors such as depression or the induction of psychological stress also promoted DNA damage, as measured by excreted DNA damage markers [2].

A major cause of DNA damage is oxidative stress, which in healthy cells is balanced by antioxidants. However, this process is often deregulated in disease progression. Psychological stress has been linked to an increase in DNA damage through the production of reactive oxygen/nitrogen species (ROS/RNS) and the induction of oxidative stress. In healthy tissue and cancer cell lines, acute exposure to high levels of cortisol-induced production of ROS/RNS. Sustained exposure induced DNA damage and repair pathways, indicating a burden of oxidative stress on the cell. Inhibition of reactive species catalyzing enzymes, as well as the GR, abrogated ROS/RNS production and DNA damage [3].

In the context of cancer, cells are often mutated to cope with the high levels of oxidative stress generated from increased mitochondrial respiration and cellular turnover. Although conversely this can also lead to defections in DNA repair mechanisms which render cells more sensitive to oxidative stress, thus succumbing to further genomic instability. It has been proposed that increased oxidative stress in primary tumors is therefore a driver of metastatic cell dissemination as an escape mechanism [4,5].

In mouse models of cancer, repeated induction of the psychological stress response - mimicking chronic stress - elicited a sustained elevation of circulating stress hormones and promoted metastatic spread [3,6]. Through activation of the

GR, synthetic glucocorticoids also significantly increased metastatic colonization in patient-derived breast cancer models [7]. In profiling circulating tumor cells (CTCs) that have the propensity to seed metastatic niches, the glucocorticoid receptor was found to be highly expressed, suggesting these cells are sensitive to fluctuations in GC levels [8].

In normal tissues, the fine balance of oxidative stress and antioxidants is maintained through complex feedback systems. The tumor suppressor BRCA1 - mutations which are heavily implicated in breast cancer susceptibility - can control cellular response to ROS through activation of the antioxidant NRF2 [9]. The unliganded GR has been shown to positively regulate BRCA1 through binding to the promotor and increased expression in mammary epithelial cells. However, upon GC stimulation GR is lost from the promotor and BRCA1 expression decreases [10]. As such, release of cortisol through the stress response could simultaneously induce DNA damage through oxidative stress and reduce the antioxidant capacity of the cells.

Although we have focused on cancer, stress hormones can negatively impact other diseases. Glucocorticoids have been implicated as cardiovascular risk factors [11], and through oxidative stress cause amyloid β peptide toxicity leading to increased risks of dementia and Alzheimer's disease [12]. Drawing together these ideas can conceivably link the effects of stress on disease initiation and progression to the genotoxicity of oxidative stress.

■ REFERENCES

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M.; Gershenson, D. M.; Kundra, V.; Lopez-Berestein, G.; Lutgendorf, S. K.; Cole, S. W.; Sood, A. K. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. Nature Medicine 2006, 12 (8), 939−944. (7) Obradović, M. M. S.; Hamelin, B.; Manevski, N.; Couto, J. P.; Sethi, A.; Coissieux, M.-M.; Münst, S.; Okamoto, R.; Kohler, H.; Schmidt, A.; Bentires-Alj, M. Glucocorticoids promote breast cancer metastasis. Nature 2019, 567 (7749), 540−544. (8) Diamantopoulou, Z.; Castro-Giner, F.; Schwab, F. D.; Foerster, C.; Saini, M.; Budinjas, S.; Strittmatter, K.; Krol, I.; Seifert, B.; Heinzelmann-Schwarz, V.; Kurzeder, C.; Rochlitz, C.; Vetter, M.; Weber, W. P.; Aceto, N. The metastatic spread of breast cancer accelerates during sleep. Nature 2022, 607 (7917), 156−162. (9) Gorrini, C.; Baniasadi, P. S.; Harris, I. S.; Silvester, J.; Inoue, S.; Snow, B.; Joshi, P. A.; Wakeham, A.; Molyneux, S. D.; Martin, B.; Bouwman, P.; Cescon, D. W.; Elia, A. J.; Winterton-Perks, Z.; Cruickshank, J.; Brenner, D.; Tseng, A.; Musgrave, M.; Berman, H. K.; Khokha, R.; Jonkers, J.; Mak, T. W.; Gauthier, M. L. BRCA1 interacts with Nrf2 to regulate antioxidant signaling and cell survival. J. Exp Med. 2013, 210 (8), 1529−44. (10) Ritter, H.; Antonova, L.; Mueller, C. R. The unliganded glucocorticoid receptor positively regulates the tumour suppressor gene BRCA1 through GABP beta. Molecular Cancer Research 2012, 10, 558. (11) Steptoe, A.; Kivimäki, M. Stress and cardiovascular disease. Nature reviews. Cardiology 2012, 9 (6), 360−70. (12) Ouanes, S.; Popp, J. High Cortisol and the Risk of Dementia and Alzheimer's Disease: A Review of the Literature. Frontiers in aging neuroscience 2019, 11, 43.

1 - From the text it is correct to assert that:

a) Physical phenomena are quite distinct from psychological phenomena, particularly, because the latter has no physical origin.

b) To take care of sick or disabled persons is always rewarding.

c) Glucocorticoids are produced as protective hormones against psychological stress.

d) Glucocorticoids have different types of receptors than catecholamines.

e) Illness is always caused by psychological tensions.

2 - The major problems with cancer development are:

a) Tumors cannot adapt to oxidative stress.

b) The overproduction of reactive species can further increase the genomic instability in cancer cells.

c) Oxidative stress does not have a role in metastasis.

d) Stress excess can protect mammals from metastasis development.

e) Metastases usually cause oxidative stress, which produces further instability in the normal DNA.

3 - The time course of cancer induction is usually associated with the cumulative dose of a given carcinogen. Considering this affirmation and the article “Genotoxicity of Stress” we can state that:

a) Catecholamines are powerful carcinogens in humans.

b) Glucocorticoids are blockers of carcinogens in fibroblasts.

c) The time course of cancer induction can be modulated *in vitro* by blocking or stimulating glucocorticoids receptors.

d) Mental stressors can activate directly tumorigenicity without the participation of glucocorticoids or catecholamines.

e) Catecholamines have no physiological roles in mammals.

4 - Normal cellular physiology is dependent on:

a) Very active antioxidant systems, which usually produce reductive stress.

b) Activation of NRF2 by mutated BRCA1.

c) NRF2 is part of a fine balance between oxidative stress and antioxidant responses.

d) Glucocorticoids do not modulate oxidative stress or antioxidant responses.

e) Deletion GR makes cells immortal.

5 - The main objective of the study “Genotoxicity of Stress” was to demonstrate that:

a) DNA damage response pathways are involved in the activation of exacerbated rates of mutation in the DNA.

b) To demonstrate that catecholamines are critical in cancer development.

c) Associating psychological stress with genotoxicity.

d) Chromatography by Gas (CG) can be used to detect damage in DNA.

e) To demonstrate that mental tension does not have a physical basis.

6 - The best linkage to DNA damage is:

a) Mutation.

b) Genomic stability.

c) Replication of DNA.

d) Healthy genome.

e) Oxidative stress.

7 - The main cause of oxidative stress in cancer cells are:

a) Activation of antioxidant pathways.

b) Psychological stress.

c) Excessive production of reactive species.

d) Blockage of glucocorticoid receptors.

e) DNA instability.

8 - In mouse, literature data supports a role for glucocorticoids in:

a) Synthetic cancer development.

b) Psychological stress and metastasis susceptibility.

c) Blockage of glucocorticoid receptors.

d) Direct activation of catecholaminergic receptors (CRs).

e) Activation of synthetic glucocorticoid synthesis pathways.

9 - Glucocorticoids are involved in cancer regulation by :

a) Interacting with β-AR.

b) Blocking GR.

c) Indirectly modulating BRCA1.

d) Directly activating the BRCA1 promotor.

e) Degrading oxidative stress and antioxidants.

10 - The main conclusion of the article “Genotoxicity of Stress” is that:

a) Oxidative stress is important to good health.

b) Cancer can cause Alzheimer’s diseases.

c) Glucocorticoids are the unique link between Alzheimer’s disease and heart problems.

d) Psychological stress may be involved in different types of chronic diseases.

e) Antioxidant supplements are critical for preventing cancer.

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Nome do candidato:

FOLHA RASCUNHO

Marque com um "X" a resposta correspondente em cada questão.

Question	A	B	C	D	E
1					
2					
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FOLHA DE RESPOSTAS DEFINITIVA.

A marcação deve ser feita com caneta azul ou preta.

Marque com um "X" a resposta correspondente em cada questão.

Question	A	B	C	D	E
1					
2					
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