The Genotoxicity of Stress

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Abstract

Higher stress and anxiety levels are often reported globally. Whilst anecdotal evidence has attributed a myriad of health conditions to stress, the mechanisms are often overlooked. Understanding the role of stress hormones on DNA damage/oxidative stress has implications for disease.

Main text

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 the 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 signalling 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 tumourigenicity 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 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 catalysing 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 tumours 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 of circulating tumour 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 tumour 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 focussed 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

1. Flint, M. S.; Baum, A.; Chambers, W. H.; Jenkins, F. J., Induction of DNA damage, alteration of DNA repair and transcriptional activation by stress hormones. *Psychoneuroendocrinology* **2007,** *32* (5), 470-479.
2. Gidron, Y.; Russ, K.; Tissarchondou, H.; Warner, J., The relation between psychological factors and DNA-damage: A critical review. *Biological Psychology* **2006,** *72* (3), 291-304.
3. Flaherty, R. L.; Intabli, H.; Falcinelli, M.; Bucca, G.; Hesketh, A.; Patel, B. A.; Allen, M. C.; Smith, C. P.; Flint, M. S., Stress hormone-mediated acceleration of breast cancer metastasis is halted by inhibition of nitric oxide synthase. *Cancer Lett* **2019,** *459*, 59-71.
4. Pani, G.; Galeotti, T.; Chiarugi, P., Metastasis: cancer cell's escape from oxidative stress. *Cancer and Metastasis Reviews* **2010,** *29* (2), 351-378.
5. Aboelella, N. S.; Brandle, C.; Kim, T.; Ding, Z. C.; Zhou, G., Oxidative Stress in the Tumor Microenvironment and Its Relevance to Cancer Immunotherapy. *Cancers (Basel)* **2021,** *13* (5).
6. Thaker, P. H.; Han, L. Y.; Kamat, A. A.; Arevalo, J. M.; Takahashi, R.; Lu, C. H.; Jennings, N. B.; Armaiz-Pena, G.; Bankson, J. A.; Ravoori, M.; Merritt, W. M.; Lin, Y. G.; Mangala, L. S.; Kim, T. J.; Coleman, R. L.; Landen, C. N.; Li, Y.; Felix, E.; Sanguino, A. M.; Newman, R. A.; Lloyd, 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**, molcanres.0423.2011.
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.