

THE ROLE OF PSYCHOLOGICAL STRESS AND NITRIC OXIDE SYNTHASE INHIBITION IN BREAST CANCER

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Disclosure: The authors have declared no conflicts of interest.

Citation: EMJ Oncol. 2017;5[1]:XX-XX. Abstract Review No. ARXX.

Keywords: Breast cancer, stress, DNA damage.

Psychological stress has been implicated as a risk factor in the progression of breast cancer, however the biological mechanisms are not well understood. In animal models of psychological stress, an increase in mammary tumour burden and metastatic spread has been observed.¹ Furthermore, in breast cancer cells, the stress hormones cortisol and noradrenaline, released as part of the stress response, have been shown to promote DNA damage through the generation of reactive oxygen/nitrogen species.²

The research presented here aimed to first explore the *in vitro* effects of cortisol by measuring the induction of DNA damage and the generation of nitric oxide (NO). An *in vivo* mouse model of psychological stress was also employed to study the impact of stress on the progression of breast cancer, alongside an inhibitor of nitric oxide synthase (NOS) (L-NAME). Through pharmacological inhibition of the glucocorticoid receptor (GR), as well as selective and non-selective inhibition of NOS, this research aimed to elucidate a mechanism through which stress may impact breast cancer progression.

In mammary tumour cells treated with cortisol, an increase in both NO and DNA damage was

observed. This was abrogated with inhibition of the GR, as well as pan-inhibition of NOS and, specifically, the isoform inducible NOS (iNOS). Cortisol upregulated the expression of iNOS, a marker previously suggested as an indicator of poor survival in breast cancer.³ Induction of chronic stress in a syngeneic mouse model of breast cancer had no effect on the growth of the primary tumour; however, inhibition of NOS in stressed mice significantly decreased tumour volume compared to stress alone. A significant increase in tumour microvasculature was observed in the primary tumours, as there was an increase in metastatic sites per mouse in stressed mice, compared to the control. This was also reversed through the inhibition of NOS.

This study indicated that stress may impact tumourigenic progression through the induction of DNA damage, mediated by the release of NO. Inhibition of NOS was able to negate the effects of stress on tumour growth and metastasis, providing an insight into the potential benefits of NOS inhibitors in breast cancer treatment. However, presentation of this research at the ESMO congress raised some potential implications of inhibition of NO signalling. Primarily, these included the effects of NOS inhibition on haemodynamics, because L-NAME has been used previously in a clinical setting to increase blood pressure. In future studies, this limitation could be resolved through cotreatment with antihypertensives, as was the case in a previous study that demonstrated the growth inhibitory effects of iNOS inhibition in breast cancer.⁴

Discussion also focussed on the effects of glucocorticoid signalling in the immune system, since previous research has demonstrated that stress can adversely affect the immune response in breast cancer models, and in patients.^{5,6} Furthermore, an increase in the expression of the GR has been observed to correlate with poor prognosis in oestrogen receptor-negative breast cancer patients, indicating that glucocorticoid-mediated signalling can influence cancer progression.⁷ As such, current trials using novel GR inhibitors in breast cancer patients are underway. Future perspectives for this work would seek to use

pharmacological therapeutics, including using selective GR inhibitors in combination with NOS inhibitors, in highly stressed patients with breast cancer.

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