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Detection the Nitric Oxide Levels upon Exposure to Interferon Gamma and Dexamethasone in Chicken Lymphoid Cancer Cells

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ABSTRACT

Nitric oxide (NO) was linked to disease inflammation severity; however, it has been shown to play roles in tumor growth and tumor suppression. The aim of this study was to investigate NO regulation upon exposure of chicken lymphoid cancer (DT40) cells to interferon gamma (INFG) and dexamethasone (DEX) at different concentrations. Pretreated-DT40 cells with 1µg INFG/ml of the nutrition media were managed by adding DEX concentrations at 0.1, 1, 10, 50µM, INF+DEX group. Moreover, one group was left with no INFG and DEX treatments, (NT) group, and other was received INFG only, (INFGO) group. After 24hrs of the treatment, the levels of NO were measured in the cells by using Griess System, and the cell proliferation rate was also recorded. The findings recorded significantly (p<0.05) the lowest levels of NO in the INFGO cells in a comparison with the NT and INF+DEX cells. Moreover, the results displayed significant (p<0.05) lower levels of NO in the INF+DEX cells when only compared to those identified from the NT cells. However, INF+DEX cells at the DEX concentration 10µM showed no change in the NO levels when only compared with those from the NT cells. For the proliferation of the cells, the outcomes unveiled significant (p<0.05) lower proliferation rates in the INF+DEX cells when compared to those identified from the NT and the INFGO cells. On the other hands, the proliferation rate of the INFGO cells was significantly (p<0.05) higher than that recorded in the NT and INF+DEX cells. Thus, interferon gamma and dexamethasone play important roles in regulating the levels of nitric oxide in the cells, and that high levels of NO may suppress the progression of the tumor cells.

Keywords: Cancer progression, dexamethasone, interferon gamma, nitric oxide.

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INTRODUCTION

The nitric oxide (NO), in different physiological and pathological activities, is a widespread water-soluble free-radical gas of a short-life period that is produced endogenously. NO has recently become an agent of concern for carcinogenesis and development of tumor growth. Nevertheless, the definition of its function in cancer biology is complicated and confusing. Tumor-progressing and inhibitory properties, depending on the time, location, and dosage, are believed to be parts of the NO activities. NO was proposed for the control of various events associated with cancer, such as angiogenesis, invasion and metastasis, and apoptosis and works as an anti-oncogenic agent (Shang, Li and Li, 2002; Harada *et al.*, 2004; Ying and Hofseth, 2007).

Interferon game (IFNG), through the transcriptional regulation of related genes of the immune system, controls a wide range of cellular pathways. In the beginning of their discovery, the IFN secretion was linked to viral infection and replication in the affected cells classified originally by the cell types responsible of their secretion; however, now, they are known, based on the sequence homological characteristics and their types of receptors, as type I and type II. The type I has the basic types of IFN-α (of 14 to 20 subtypes), IFN-β, IFN-ω, and IFN-τ, which have a shared heterodimeric receptor (IFNAR of 1 and 2 chains). INFs are low-level-secreted by all types of cells; however, cells of hematopoietic types are well known for high production of IFN-α and IFN-ω, while IFN-β are highly secreted by fibroblasts and with certain amounts from macrophages after stimulation. IFN-γ is the major component of INF type II. It is not related to INF type I due to structural differences and has a completely different chromosomal locus and receptor that binds to. It can be secreted by various cell types such as CD4+ T helper cell type 1 (Th1) lymphocytes, CD8+ cytotoxic lymphocytes, and natural killer (NK) cells, NKT cells, B cells, antigen-presenting cells (APCs) (Flaishon *et al.*, 2000; Harris *et al.*, 2000; Frucht *et al.*, 2001; Jonasch and Haluska, 2001; Sen, 2001; Schroder *et al.*, 2004).

The glucocorticoid receptor (GR) has a non-oncogenic activity compared to that from other hormone receptors such as the estrogen receptor (ER) and the androgen receptor (AR) that play important actions in breast and prostate cancer progression, respectively. Dexamethasone has been used for fighting lymphoid cancer cells; however, resistance has been developed in some cancer cells. For that, thorough studies were performed to understand the mechanisms behind this resistance and how to potentiate the work of DEX (Inaba and Pui, 2010; Teuffel *et al.*, 2011; Pufall, 2015).

The aim of this study was to investigate NO regulation upon exposure of chicken lymphoid cancer (DT40) cells

to interferon gamma (INFG) and dexamethasone (DEX) in different concentrations.

MATERIALS AND METHODS

Cell line and experiment

Chicken lymphoid cancer (DT40) cell lines were used that were exposed to INFG and DEX at different concentrations. Pretreated-DT40 cells with 1µg INFG/ml of the nutrition media were managed by adding DEX concentrations at 0.1, 1, 10, 50µM, INF+DEX group. Moreover, one group was left with no INFG and DEX treatments, (NT) group, and other was received INFG only, (INFGO) group. The exposure was continued for 24hrs.

Levels of NO and cell proliferation measurement

After 24hrs of the treatment, the levels of NO were measured in the cells by using Griess System, and the cell proliferation rate was also recorded.

RESULTS

The findings recorded significantly (p<0.05) the lowest levels of NO in the INFGO cells in a comparison with the NT and INF+DEX cells. Moreover, the results displayed significant (p<0.05) lower levels of NO in the INF+DEX cells when only compared to those identified from the NT cells. However, INF+DEX cells at the DEX concentration 10µM showed no change in the NO levels when only compared with those from the NT cells, figure 1.

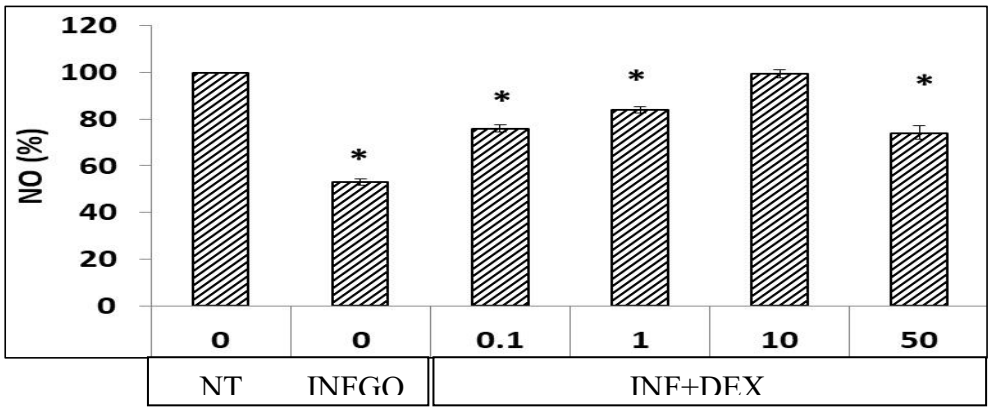

Figure 1: Nitric oxide regulation by GR upon tested compounds in DT40 cells. The findings recorded significantly (p<0.05) the lowest levels of NO in the INFGO cells in a comparison with the NT and INF+DEX cells. Moreover, the results displayed significant (p<0.05) lower levels of NO in the INF+DEX cells when only compared to those identified from the NT cells. However, INF+DEX cells at the DEX concentration 10µM showed no change in the NO levels when only compared with those from the NT cells.

For the proliferation of the cells, the outcomes unveiled significant (p<0.05) lower proliferation rates in the INF+DEX cells when compared to those identified from the NT and the INFGO cells. On the other hands, the proliferation rate of the INFGO cells was significantly (p<0.05) higher than that recorded in the NT and INF+DEX cells, figure 2.

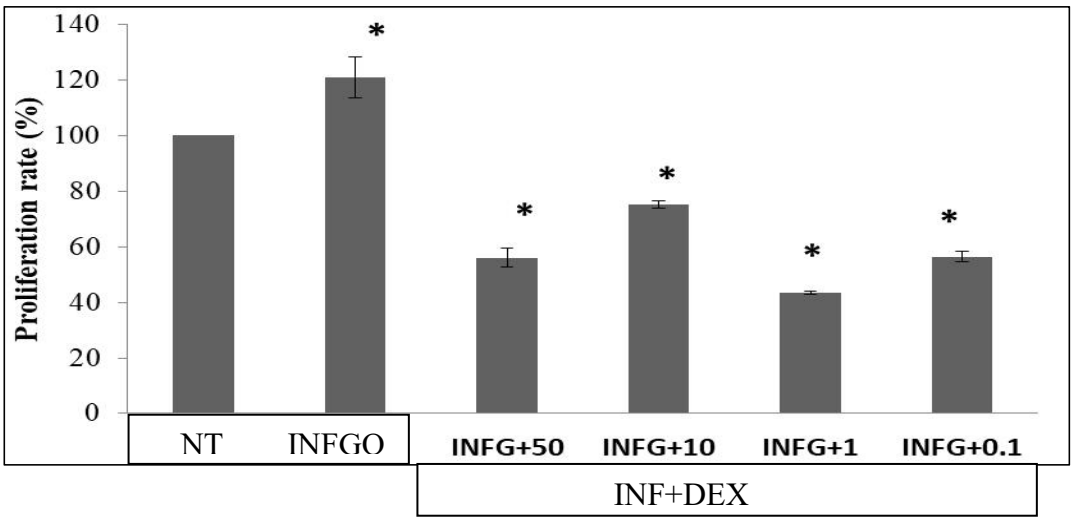

Figure 2: Effects of different doses of DEX and IFNG on DT40 cells. For the proliferation of the cells, the outcomes unveiled significant (p<0.05) lower proliferation rates in the INF+DEX cells when compared to those identified from the NT and the INFGO cells. On the other hands, the proliferation rate of the INFGO cells was significantly (p<0.05) higher than that recorded in the NT and INF+DEX cells.

DISCUSSION

The function of NO is generally beneficial as a vasorellaxant and its presence in physiological conditions determines the effect of NO. NO favors and functions as either an anti-tumor or tumor promoter. There is a big debate going on about those two activities of this gas (Vahora *et al.*, 2016).

The results identified important changes in the levels of NO in study groups. The findings recorded significantly (p<0.05) the lowest levels of NO in the INFGO cells in a comparison with the NT and INF+DEX cells. This indicates that INFG may interfere with the production of NO leading to substantial decreases in the levels of this gas in the treated cells. Interestingly, the cells treated with INFG only showed the highest proliferation rate which may approve that NO high levels are important in suppressing the cancer cell growth. The data, here, agree with Javanmard and Dana, 2012 (Javanmard and Dana, 2012) who found that high levels of INFG encouraged decreases in the levels of NO production in the human umbilical vein endothelial cells. However, a disagreement with the current study findings can be shown when reviewing the work of these authors (Javanmard and Dana, 2012) who provided significant evidence that this reduction in the levels of NO had led to the highest levels of apoptosis in the treated cells. The physiological work of NO as an apoptotic agent may be disturbed due to timing and location which why the results, here, showed differences with the above mentioned study (Shang, Li and Li, 2002; Harada *et al.*, 2004; Ying and Hofseth, 2007). Moreover, the results displayed significant lower levels of NO in the INF+DEX cells when only compared to those identified from the NT cells. However, all those levels of NO resulted in higher apoptosis rates in the treated cells when compared to those from the NT and INFGO cell groups. This indicates restored functions of DEX via GR in the presence of INFG (Inaba and Pui, 2010; Teuffel *et al.*, 2011; Pufall, 2015).

CONCLUSION

Thus, interferon gamma and dexamethasone play important roles in regulating the levels of nitric oxide in the cells, and that high levels of NO may suppress the progression of the tumor cells.

REFERENCES

1. Flaishon, L. *et al.* (2000) 'Autocrine Secretion of Interferon γ Negatively Regulates Homing of Immature B Cells', *The Journal of Experimental Medicine*, 192(9), pp. 1381–1388. doi: 10.1084/jem.192.9.1381.
2. Frucht, D. M. *et al.* (2001) 'IFN-gamma production by antigen-presenting cells: mechanisms emerge.', *Trends in immunology*, 22(10), pp. 556–60. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11574279 (Accessed: 19 October 2019).
3. Harada, K. *et al.* (2004) 'Overexpression of iNOS gene suppresses the tumorigenicity and metastasis of oral cancer cells.', *In vivo (Athens, Greece)*, 18(4), pp. 449–55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15369183 (Accessed: 19 October 2019).
4. Harris, D. P. *et al.* (2000) 'Reciprocal regulation of polarized cytokine production by effector B and T cells', *Nature Immunology*, 1(6), pp. 475–482. doi: 10.1038/82717.
5. Inaba, H. and Pui, C.-H. (2010) 'Glucocorticoid use in acute lymphoblastic leukaemia', *The Lancet Oncology*, 11(11), pp. 1096–1106. doi: 10.1016/S1470-2045(10)70114-5.
6. Javanmard, S. H. and Dana, N. (2012) 'The effect of interferon γ on endothelial cell nitric oxide production and apoptosis.', *Advanced biomedical research*. Wolters Kluwer -- Medknow Publications, 1, p. 69. doi: 10.4103/2277-9175.102973.
7. Jonasch, E. and Haluska, F. G. (2001) 'Interferon in Oncological Practice: Review of Interferon Biology, Clinical Applications, and Toxicities', *The Oncologist*, 6(1), pp. 34–55. doi: 10.1634/theoncologist.6-1-34.
8. Pufall, M. A. (2015) 'Glucocorticoids and Cancer.', *Advances in experimental medicine and biology*. NIH Public Access, 872, pp. 315–33. doi: 10.1007/978-1-4939-2895-8_14.
9. Schroder, K. *et al.* (2004) 'Interferon-γ: an overview of signals, mechanisms and functions', *Journal of Leukocyte Biology*. John Wiley & Sons, Ltd, 75(2), pp. 163–189. doi: 10.1189/jlb.0603252.
10. Sen, G. C. (2001) 'Viruses and Interferons', *Annual Review of Microbiology*, 55(1), pp. 255–281. doi: 10.1146/annurev.micro.55.1.255.
11. Shang, Z.-J., Li, J.-R. and Li, Z.-B. (2002) 'Effects of exogenous nitric oxide on oral squamous cell carcinoma: An in vitro study', *Journal of Oral and Maxillofacial Surgery*, 60(8), pp. 905–910. doi: 10.1053/joms.2002.33860.
12. Teuffel, O. *et al.* (2011) 'Dexamethasone versus prednisone for induction therapy in childhood acute lymphoblastic leukemia: a systematic review and meta-analysis', *Leukemia*, 25(8), pp. 1232–1238. doi: 10.1038/leu.2011.84.
13. Vahora, H. *et al.* (2016) 'The Potential Role of Nitric Oxide in Halting Cancer Progression Through Chemoprevention', *Journal of Cancer Prevention*. Korean Society of Cancer Prevention, 21(1), p. 1. doi: 10.15430/JCP.2016.21.1.1.
14. Ying, L. and Hofseth, L. J. (2007) 'An Emerging Role for Endothelial Nitric Oxide Synthase in Chronic Inflammation and Cancer', *Cancer Research*, 67(4), pp. 1407–1410. doi: 10.1158/0008-5472.CAN-06-2149.