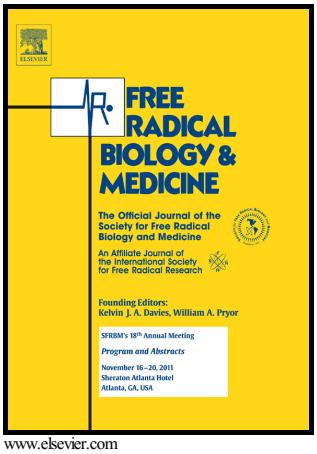

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Alteration of Nrf2 and Glutamate Cysteine Ligase expression contribute to lesions growth and fibrogenesis in ectopic endometriosis

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Abstract

The redox-sensitive nuclear factor erythroid-derived 2-like 2 (NRF2) controls endogenous antioxidant enzymes' transcription and protects against oxidative damage which is triggered by inflammation and known to favor progression of endometriosis. Glutamate cysteine ligase (GCL), a target gene of NRF2, is the first enzyme in the synthesis cascade of glutathione, an important endogenous antioxidant. Sixty-one patients, with thorough surgical examination of the abdominopelvic cavity, were recruited for the study: 31 with histologically-proven endometriosis and 30 disease-free women taken as controls. Expressions of NRF2 and GCL were investigated by quantitative RT-PCR and immunohistochemistry in eutopic and ectopic endometria from endometriosis-affected women and in endometrium of disease-free women. Ex vivo stromal and epithelial cells were extracted and purified from endometrial and endometriotic biopsies to explore expression of NRF2 and GCL in both stromal and epithelial compartments by western blot. Finally, in order to strengthen the role of NRF2 in endometriosis pathogenesis, we evaluated the drop of NRF2 expression in a mouse model of endometriosis using NRF2 knockout ($NRF2^{-/-}$) mice. The mRNA levels of NRF2 and GCL were significantly lower in ectopic endometria of endometriosis-affected women compared to eutopic endometria of disease-free women. The immunohistochemical analysis confirmed the decreased expression of both NRF2 and GCL in ectopic endometriotic tissues compared to eutopic endometria of endometriosis-affected and disease-free women. Immunoblotting revealed a significant decreased of NRF2 and GCL expression in epithelial and stroma cells from

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