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Reactive oxygen species controls endometriosis progression

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Abstract

Endometriosis is associated with chronic inflammation, and reactive oxygen species (ROS) are proinflammatory mediators that modulate cell proliferation. We have investigated whether the dysregulation of ROS production in endometriotic cells correlates with a pro-proliferative phenotype and can explain the spreading of this disease. Stromal and epithelial cells were purified from ovarian endometrioma and eutopic endometrium from 14 patients with endometriosis to produce four primary cell lines from each patient. ROS production, detoxification pathways, cell proliferation, and mitogen-activated protein kinase pathway activation were studied and compared with epithelial and stromal cell lines from 14 patients without endometriosis. Modulation of the proliferation of endometriosis by N-acetyl-cysteine, danazol, and mifepristone was tested in vitro and in 28 nude mice implanted with endometriotic tissue of human origin. Endometriotic cells displayed higher endogenous oxidative stress with an increase in ROS production, alterations in ROS detoxification pathways, and a drop in catalase levels, as observed for tumor cells. This increase in endogenous ROS correlated with increased cellular proliferation and activation of ERK1/2. These phenomena were abrogated by the antioxidant molecule N-acetyl-cysteine both in vitro and in a mouse model of endometriosis. Human endometriotic cells display activated pERK, enhanced ROS production, and proliferative capability. Our murine model shows that antioxidant molecules could be used as safe and efficient treatments for endometriosis.