

MITOCHONDRIA RELATED CELL DEATH BY CYTOKINES AND ITS PREVENTION BY ESTROGEN IN ESTROGEN RECEPTOR EXPRESSED RHEUMATOID ARTHRITIS SYNOVIAL FIBROBLASTS

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We examined the expressions of estrogen receptor (ER), the production and activity of reactive oxygen species (ROS), nitric oxide (NO) synthesis, lipid peroxidation and apoptosis following a cytokine treatment in primary fibroblast cell lines which have been established from human synovial tissues of rheumatoid arthritis (RA) patients. Two cell lines, which expressed the most, and two cell lines, which expressed the least were selected among 9 cell lines, and were used for this study. Cells, incubated with cytokines (IL-1b, TNF-a, IFN-g) with or without estrogen, were examined to observe generations of ROS, NO, lipid peroxidation and apoptotic cell death. The results showed that cytokines stimulation on synovial fibroblasts increased the intracellular mitochondrial ROS and NO generations, lipid peroxidation product. Combined treatment of cytokines and estrogen for the high ERa expressed fibroblasts decreased the mitochondrial ROS and NO generations, lipid peroxidation product and prevented subsequent apoptotic cell death, although the low expressed ERa cells did not show the substantial change. Examinations of the levels of iNOS mRNA confirmed that the expression was dependent on the NO levels. These results suggest that both mitochondrial ROS and NO are key players to RA pathogenesis and estrogen plays an important role in protecting cells against cytokine-induced cell death by controlling the generations of ROS, NO and lipid peroxidation. These results also suggest that mitochondria, as the initial trigger, control the subsequent events to induce apoptosis in RA cells.