Adenosine triphosphate activates mitogen-activated protein kinase in pre-neoplastic and neoplastic ovarian surface epithelial cells.

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摘要

Abstract

To investigate the role of ATP in ovarian tumorigenesis, the present study examined the expression of the P2U purinoceptor (P2U-R) and effect of ATP on growth stimulation in pre-neoplastic and neoplastic ovarian surface epithelial (OSE) cells. The immortalized OSE (IOSE) cell lines, including IOSE-29 (pre-neoplastic), IOSE-29EC (neoplastic), and OVCAR-3 (ovarian adenocarcinoma cell line) were used. Our results indicated that P2U-R mRNA was expressed and that ATP exerted a growth-stimulatory effect in IOSE-29, IOSE-29EC, and OVCAR-3. To investigate the mechanism of the growth-stimulatory effect, the activation of mitogen-activated protein kinases (MAPKs) by ATP was examined. Treatment with ATP resulted in MAPK activation in IOSE-29 and IOSE-29EC cells, whereas the stimulatory effect of ATP in cellular proliferation and MAPK activation was completely abolished in the presence of PD98059 (an MAPK/ERK kinase inhibitor) and staurosporin (a protein kinase C inhibitor), suggesting that the growth stimulatory effect of ATP is mediated via protein kinase C-dependent MAPK activation in pre-neoplastic and neoplastic OSE cells. In a time-dependent study, ATP significantly increased MAPK activity at 5–20 min in IOSE-29 cells. Activated MAPK declined to control levels after 20 min in these cells. Treatment with ATP significantly induced MAPK activation after 5 min and was sustained for 60 min in IOSE-29EC cells. In addition, treatment with ATP resulted in substantial phosphorylation of Elk-1, the Ets family transcriptional factor, confirming that ATP action is mediated by activation of MAPK. In conclusion, we have demonstrated that P2U-R was expressed and that ATP induced growth stimulation in IOSE and OVCAR-3 cells. Furthermore, treatment with ATP resulted in the activation of an MAPK cascade

and phosphorylation of Elk-1 in IOSE-29 and IOSE-29EC cells. These results suggest that the MAPK cascade may be involved in growth stimulation in response to ATP in pre-neoplastic and neoplastic OSE cells.