# p38α MAPK Mediates 17β-Estradiol Inhibition of MMP-2 and -9 Expression and Cell Migration in Human LoVo Colon Cancer Cells

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**Abstract**

Epidemiological studies demonstrate that the incidence and mortality rates of colorectal cancer in women are lower than in men. However, it is unknown if 17β-estradiol (E2) treatment is sufficient to inhibit cell proliferation and cell migration in human colon cancer cells. Up-regulation of urokinase plasminogen activator (uPA), tissue plasminogen activator (tPA) and matrix metallopeptidases (MMPs) is reported to associate with the development of cancer cell mobility, metastasis, and subsequent malignant tumor.In the present study, we treated human LoVo colon cancer cells with E2 to explore whether E2 down-regulates cell proliferation and migration, and to identify the precise molecular and cellular mechanisms behind the down-regulatory responses. Here, we found that E2 treatment decreased cell proliferation and cell cycle-regulating factors such as cyclin A, cyclin D1 and cyclin E. At the same time, E2 significantly inhibited cell migration and migration-related factors such as uPA, tPA, MMP-2 and MMP-9. However, E2 treatment showed no effects on upregulating expression of plasminogen activator inhibitor-1 (PAI-1), tissue inhibitor of metalloproteinase-1, -2, -3 and -4 (TIMP-1, -2, -3 and -4). After administration of inhibitors including QNZ (NFκB inhibitor), LY294002 (Akt activation inhibitor), U0126 (ERK1/2 inhibitor), SB203580 (p38 MAPK inhibitor) or SP600125 (JNK1/2 inhibitor), E2-downregulated cell migration and expression of MMP-2 and MMP-9 in LoVo cells is markedly inhibited only by p38 MAPK inhibitors, SB203580. Application of specific target gene siRNA (ERα, ERβ, p38α and p38β) to LoVo cells further confirmed that p38 MAPK mediates E2/ERs inhibition of MMP-2 and -9 expression and cell motility in LoVo cells.

Collectively, these results suggest that E2 treatment down-regulates cell proliferation by modulating the expression of cyclin A, cyclin D1 and cyclin E. E2 treatment simultaneously impaired cell migration by inhibiting the expression of uPA, tPA, MMP-2 and MMP-9 through E2/ERs p38α MAPK signaling pathway in human LoVo colon cancer cells.

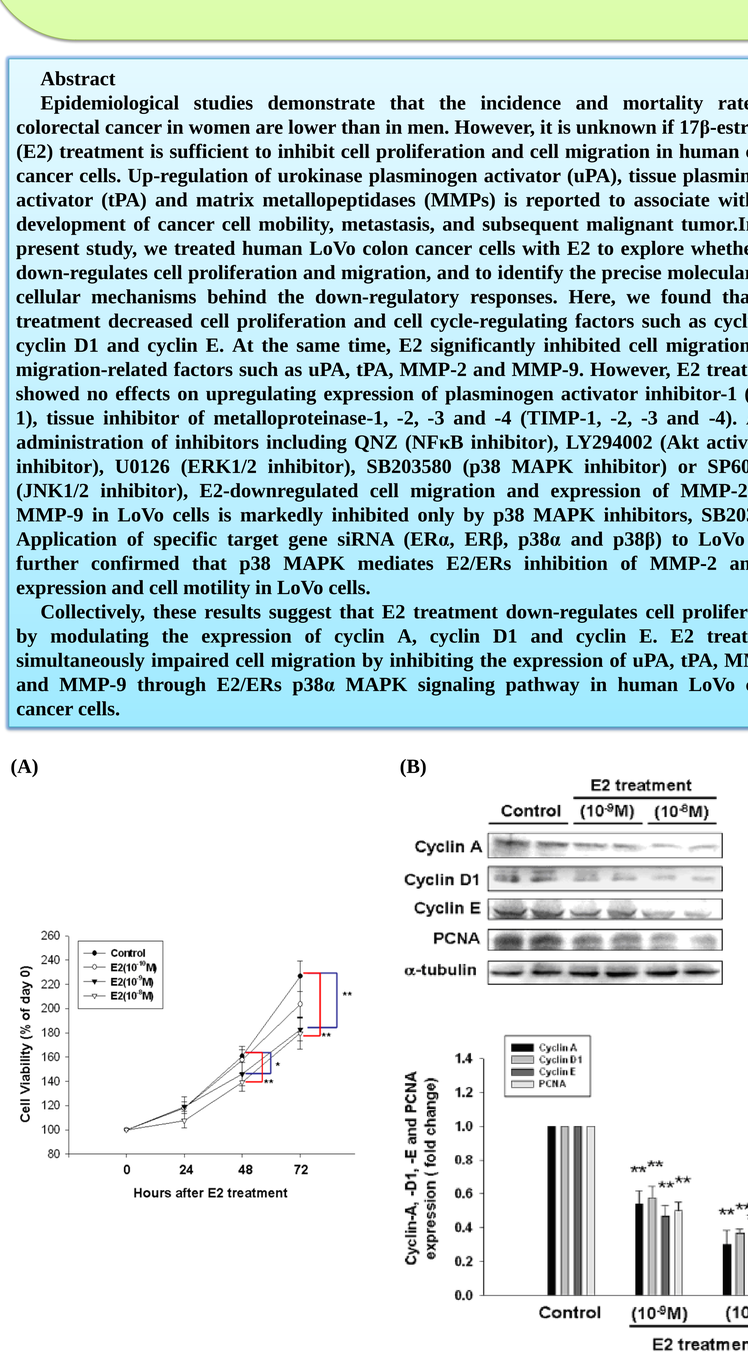


Fig. 1. 17β-Estradiol impairs cell proliferation in human LoVo colon cancer cells




Fig. 2. 17β-Estradiol inhibits cell migration in human LoVo colon cancer cells




Fig. 3. 17β-Estradiol reduces protein level of uPA, tPA, MMP-2 and MMP-9 in LoVo cells

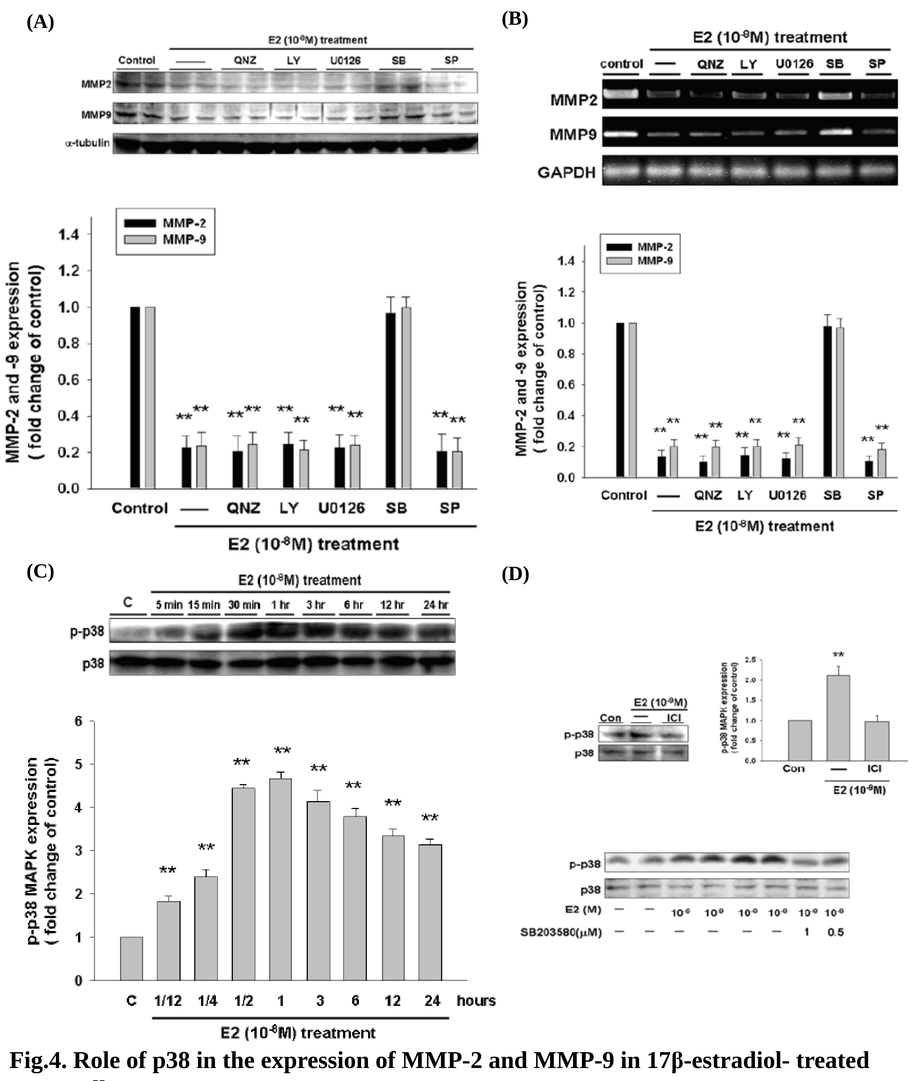


Fig.4. Role of p38 in the expression of MMP-2 and MMP-9 in 17β-estradiol- treated LoVo cells

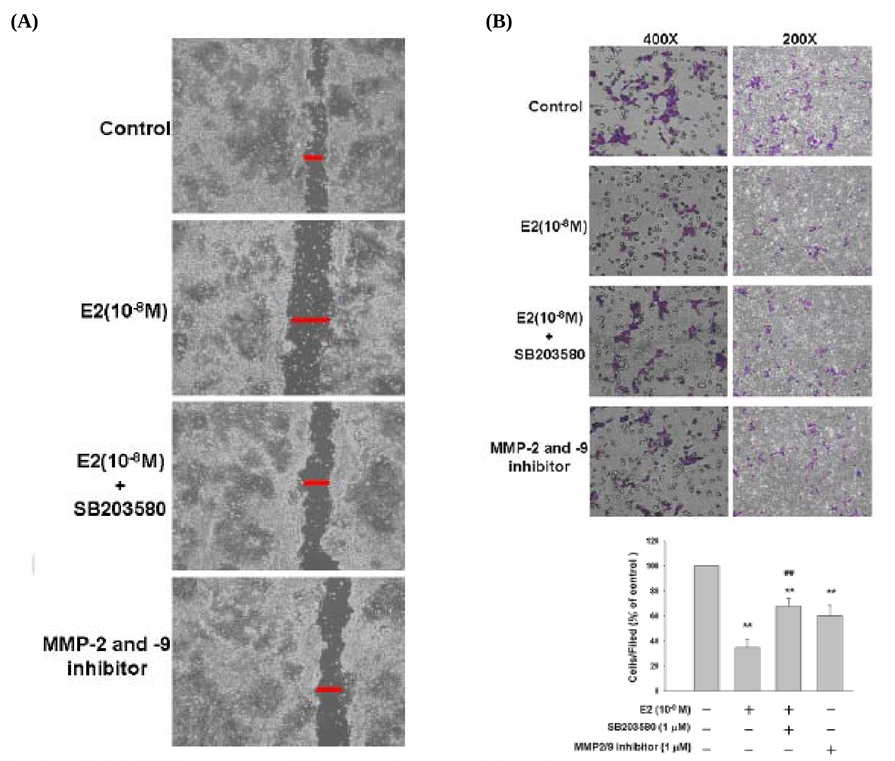


Fig. 5. p38 MAPK mediates 17β-estradiol inhibition of cell migration in human LoVo cells

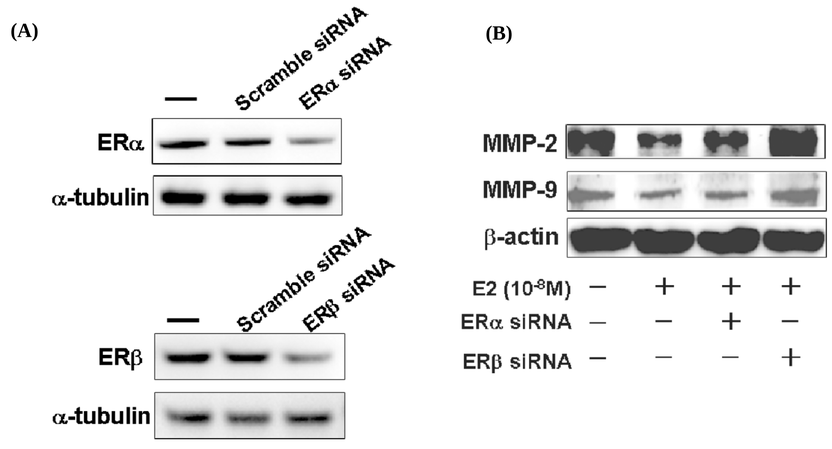


Fig.6. ERs mediates 17β-estradiol inhibition of MMP-2 and MMP-9 in human LoVo cells

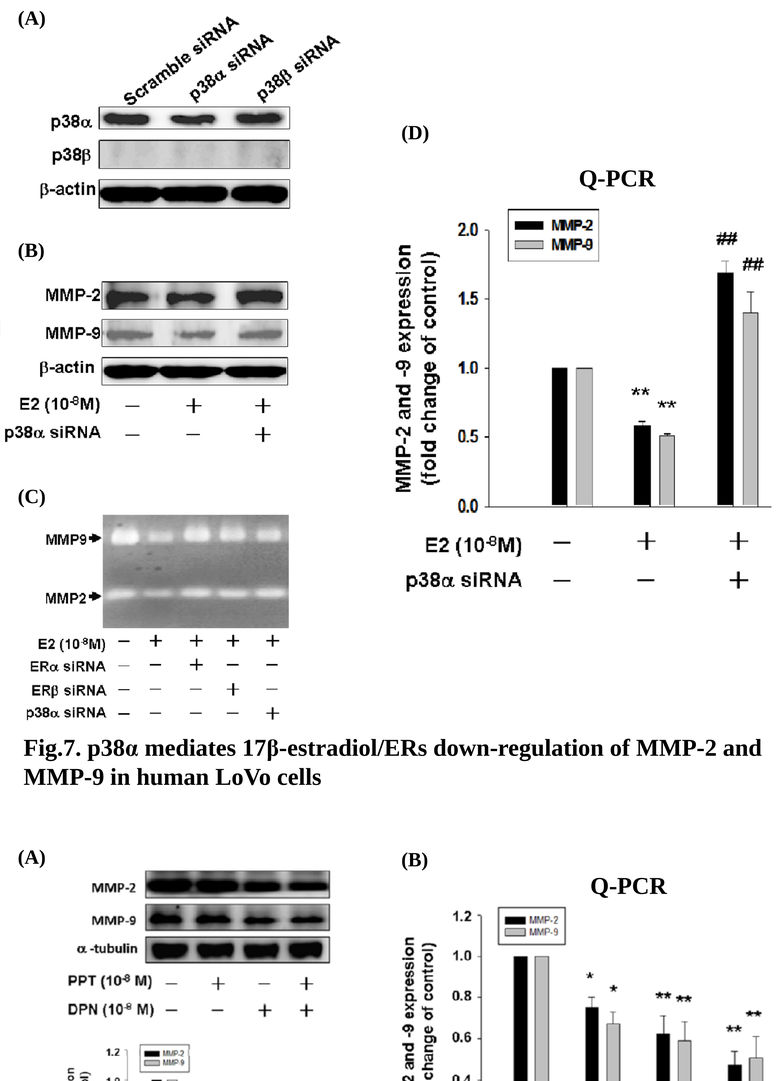


Fig.7. p38α mediates 17β-estradiol/ERs down-regulation of MMP-2 and MMP-9 in human LoVo cells

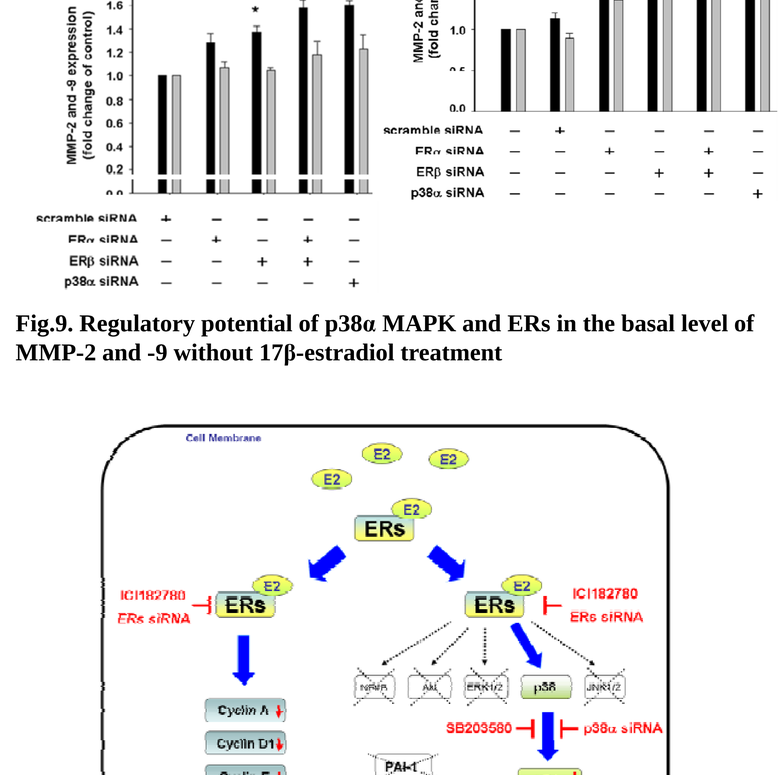


Fig.8. PPT and DPN inhibit expression of MMP-2 and MMP-9 in LoVo cells

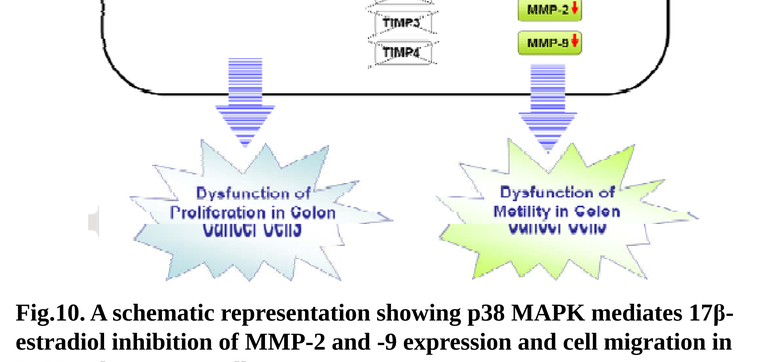


Fig.9. Regulatory potential of p38α MAPK and ERs in the basal level of MMP-2 and -9 without 17β-estradiol treatment




Fig.10. A schematic representation showing p38 MAPK mediates 17β-estradiol inhibition of MMP-2 and -9 expression and cell migration in LoVo colon cancer cells