This study is aimed to determine the impact of MRI features such as tumor volume, myometrial invasion and extent of nodal involvement in the outcome of patients with locally advanced cervix cancer treated with CRT.
Materials and Methods: 97 patients underwent exam under anesthesia and had MRI staging investigations prior to entry in a prospective study of CRT between 1999 and 2006. Characteristics of the patients are as follows: median age was 52 years, FIGO stage was IB/IIA in 38, IIB in 32, IIIA/B in 21, and IVA in 6 patients. Tumor characteristics were assessed as follows: clinical tumor size, tumor size by imaging, tumor volume by imaging, depth of myometrial extension >2 cm vs. <2 cm. The number of lymph nodes at MRI were classified as: number of nodes >5 mm, number of nodes >8 mm, number of nodes >10 mm, and maximum nodal diameter, measured along the shortest dimension. Pelvic radiation was given to a dose of 45−50 Gy in 25 fractions followed by 40 Gy using LDR or PDR brachytherapy. Weekly cisplatin was given at a dose of 40 mg/m^2 for 5 courses.
Results: After completing CRT treatment 77.5% of the patients had complete response. The disease free survival (DFS) at 3 years was 53%. In the multivariate analysis of tumor characteristics the depth of myometrial invasion >2 cm was the strongest predictor of DFS (HR 3.42, 95% CI 1.82−6.45, p = 0.00014) when compared to the other tumor variables. The multivariate analysis of lymph node characteristics showed that the maximum nodal diameter, as well as the number of nodes were important predictors for DFS. When these three variables were analysed together only myometrial invasion >2 cm and number of lymph nodes >8 mm were predictors of DFS (HR 2.93, 95% CI 1.44−5.95, p = 0.0029, and HR 1.24, 95% CI 1.09−1.40, p = 0.00069 respectively)
Conclusions: Depth of myometrial invasion measured using MR imaging appears to be a better predictor of DFS than tumor volume in women with locally advanced cervix cancer.
The number of enlarged nodes adds significant prognostic information above that provided by diagnosis of nodal involvement alone. These results are consistent with data from surgical staging in cervix and other cancers, may improve prognostication and treatment selection, and demonstrate the importance of MR imaging in the staging of these tumors.

5017 POSTER

p70S6K induces epithelial to mesenchymal transition in human ovarian cancer cells through upregulation of Snail

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Background: Epithelial ovarian cancer is the most lethal gynecological malignancy and is a highly metastatic cancer characterized by widespread peritoneal dissemination and ascites. The 70 kDa S6 kinase (p70^{S6K}) is a downstream effector of the phosphatidylinositol 3-kinase/AKT/mTOR pathway, which is frequently activated in human ovarian cancer. We recently demonstrated a novel role of p70^{S6K} in the invasion of ovarian cancer cells. Since epithelial-to-mesenchymal transition (EMT) is a critical step contributing to tumor invasiveness, we hypothesized that p70^{S6K} activation induced molecular alterations that mediate EMT.
Materials and Methods: To examine the roles of p70^{S6K}, constitutively active forms of p70^{S6K} were transfected into the ovarian cancer cell lines, and the consequence of their transfection was investigated. Optical microscopy was used to assess changes in cell morphology and behavior. Western blot, reverse transcription (RT)-PCR, and reporter gene assays were employed to measure the expression and activity of epithelial and mesenchymal markers.
Results: We showed that ovarian cancer cells expressed constitutively active p70^{S6K} underwent phenotypic changes consistent with EMT: the cells lost epithelial cell morphology, acquired fibroblast-like properties, and showed reduced intercellular adhesion. Western blot and RT-PCR revealed strong reduction of the epithelial marker E-cadherin expression and activation of mesenchymal markers vimentin and N-cadherin in p70^{S6K}-expressing cells. Consistently, p70^{S6K} downregulation by small interfering RNA (siRNA) or the specific mTOR/p70^{S6K} inhibitor rapamycin caused the reversion to an epithelial phenotype, in which E-cadherin was relocalized to the plasma membrane. In addition, active p70^{S6K} induced upregulation of Snail, a repressor of E-cadherin and an inducer of the EMT, which could be reverted by siRNA-mediated repression of p70^{S6K}, indicating that p70^{S6K}-induced EMT depends on Snail. We also showed that p70^{S6K} enhanced Snail activity through inactivation of glycogen synthase kinase 3beta (GSK3β), as expression of constitutively active GSK3β blocked p70^{S6K}-dependent Snail activation.
Conclusion: Our study indicates, for the first time, that activation of p70^{S6K} mediates EMT through upregulation of Snail via GSK3β. These findings not only expand the spectrum of biological activities of p70^{S6K} but also suggest that therapeutic inhibition of p70^{S6K} may be a useful strategy to control ovarian tumor invasion and metastasis (supported by RGC HKU7599/05M).

5018 POSTER

p53 dominant-negative mutant R273H promotes invasion and migration of human endometrial cancer HHUA cells

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Background: Dominant negative (DN) mutations of tumor suppressor p53 (TP53) are clinically associated with cancer progression and metastasis of endometrial malignancy. In this study, we used human endometrial cancer cells HHUA expressing wt p53, to clarify the role and mechanism of DN mutants of p53 in endometrial tumorigenesis.
Materials and Methods: We generated cells that stably co-expressing wt p53 and R273H DN mutant p53 (273H cells) and cells stably co-expressing wt p53 and R213Q recessive mutant p53 (213Q cells). Their invasion and migration capabilities were compared with parent HHUA cells. We also assessed the expression of wt p53 target genes Maspin, PAI-1 and KAI1 in these cell lines. Moreover, induction of wt p53 function by Adriamycin and stable expression of R273H in p53-null SK-OV-3 and Saos-2 cells were used to determined whether R273H functions as a gain-of-function mutant, contributing an invasive phenotype in HHUA cells.
Results: 273H cells showed markedly increased invasion and migration potentials, and displayed reduced Maspin, PAI-1 and KAI1 mRNA expressions as compared with 213Q and parent cells. The wt p53 induction by Adriamycin resulted in the inhibition of the invasion capacity in association with the up-regulation of Maspin, PAI-1 and KAI1 to a far greater degree in 213Q and wt cells than in 273H cells. R273H expression in SK-OV-3 and Saos-2 cells did not significantly affect cell invasion activities.
Conclusions: Our results suggest that DN mutant TP53 R273H may promote endometrial metastasis by increasing invasion and migration of tumor cells through the mutant p53 transdominance mechanisms.

5019 POSTER

Growth inhibition and FAS-mediated apoptosis in human endometrial cancer cells by treatment with isoliquiritigenin (ISL)

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Background: Endometrial Cancer is the 3rd most common gynecologic malignancies in Korea. Despite the fact that endometrial cancer is so common, innovative research has traditionally been lacking. Isoliqiritigenin(ISL) is a calchone flavonoid, present in licorice, shallot and bean sprouts, has cancer-preventing properties and often used in Oriental medicine. ISL is one of components in Spatholobus subrectus Dunn in the literature. In the present study we used ISL to determine its effect on cell proliferation and cell cycle progression in human endometrial cancer cell line, HEC1-A.
Materials and Methods: Endometrial cancercells(HEC-1-A) were treated with ISL. Cell viability analysis was analyzed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTS) assay and Flow cytometry was performed to ascertain the effects ISL. Expression of cell cycle related proteins and apoptosis related proteins were evaluated by Western blot analysis.
Results: Cell viability was significantly influenced by ISL treatment in a dose-dependent manner. Flow cytometry results showed that ISL induced Sub G1 and G2/M arrest. To reiterate this observation, DNA fragmentation assay was carried out and apoptosis was detected. Activation of caspase-3 and caspase-8, down-regulation of Bcl-2, with concomitant increase in Bax and FAS was observed. ISL treatment of endometrial cancer cells resulted in a concentration-dependent cell death induced via the FAS receptor-apoptosis cascade mechanism.
Conclusions: These results suggest that ISL treatment in endometrial cancer cells leads to growth inhibition and that this inhibition is mediated at least in part by apoptosis via the FAS death receptor induced caspase-8 cascade pathway. These results suggest that ISL will be a promising agent for use in chemopreventive or therapeutics against human uterine endometrial cancer.