Uterine cancer and ezrin expression

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Today, almost 20% of female cancers are gynecological in nature. In particular, uterine cervical cancer and endometrial cancer (which have been intensively studied) seriously compromise female health. One of the ezrin-radixin-moesin (ERM) proteins, ezrin, has been associated with cancer in prior studies, including the two cancers mentioned above. Ezrin expression increases, as does the expression of other factors, in uterine cervical cancer; ezrin may promote cancer development by influencing the actions of the other factors. Also, an increase in ezrin level contributes to the development of diseases such as endometrial cancer.

Key Words: Cervical intraepithelial neoplasia, endometrial neoplasms, neurofibronin 2, uterine cervical neoplasms

Of all female cancers, about 23% are gynecological in nature.¹ In 2014, the American Cancer Society (ACS) reported that 67,770 women in the USA had cervical and endometrial cancer, and 14,270 had died in that year. Also, the Ministry of Health and Welfare (MOHW) of Korea confirmed that uterine cancer was becoming more prevalent. In addition, the statistics in 2012 in comparison to 2000, the uterine cervix cancer patients increased to 40%. Gynecological cancers (particularly uterine cervical and endometrial cancer) have received a great deal of attention in terms of diagnosis, development, and prevention. Ezrin-radixin-moesin (ERM) proteins may be more highly expressed in cancer patients than others.² The ERM proteins affect the cytoskeletal actin, in turn modifying cell signaling, migration, morphogenesis, proliferation, invasion, and metastasis. Ezrin links the membrane with the actin cytoskeleton. The ERM proteins play roles in cell adhesion and migration by engaging with relevant cellular networks.³ Mutation of the ezrin-encoding gene, and abnormal protein expression, have been observed in many types of cancer, including that of the stomach, pancreas, lung, breast, and vagina.⁴⁻⁹ In the present study, we explore the association between
ezrin levels and uterine cancers.

1. ERM proteins and cancer

ERM proteins affect the actin-based cytoskeleton, influencing epithelial cell growth and membrane functions. Gene knockout and mutation experiments have shown that the ERM proteins are located in junctions between epithelial cells. The membrane receptor for ezrin can be stimulated by various ligands triggering cell migration, in turn affecting ezrin action. ERM proteins in epithelial cell membrane junctions cause Rac 1 to become associated with the membrane: Rac 1 acts through the CD44 receptor to affect the actin cytoskeleton, promoting cell motility, which in turn influences ERM protein activities. ERM proteins are initially maintained in an inactive state (linked C-terminus-to-N-terminus) in the cytoplasm. Phosphorylation of threonine and tyrosine trigger protein activation and transfer to the cell membrane, where the protein binds directly or indirectly to F-actin in the membrane. Reduction in tumor suppressor levels trigger ezrin overexpression and activate PI3K, in turn stimulating cell survival activities. Beta-catenin interacts with ezrin and the Fes kinase to compromise between-cell contact. Thus, cancer cell survival and proliferation are promoted: cancers may migrate and invade surrounding cells and tissues. ERM protein expression is very closely associated with cancer; ezrin overexpression promotes cancer development in general, and (probably) cervical and endometrial cancer in particular.

2. Ezrin and the uterine cervix

Cervical cancer is usually (80%) caused by human papillomavirus (HPV) infection and develops 7-15 years after such infection. Ezrin, which is not expressed in normal tissue, was found in the apical membranes and around the nuclei of cancer cells. After HPV infection, ezrin expression in the cervix was higher than that of cervical intraepithelial neoplasms and normal non-infected cervical epithelium. In addition, ezrin was more expressed early-stage than late-stage tumor in development and metastasis. Thus, ezrin plays no role in the normal cervix, but is activated to contribute to cancer development. Also, the cyclin-dependent kinase inhibitor p16NK4a, E-cadherin, and beta-catenin, are not expressed in normal cervical squamous epithelium. However, upon ezrin dephosphorylation, p16NK4a became colocalized with CDK4 and CDK6 in hrHPV-associated dysplastic lesions similar to those of cervical cancer. E-cadherin and beta-catenin levels varied
with lesional severity, suggesting that the activities of p16NK4a, E-cadherin and beta-catenin contribute to the ezrin-induced damage associated with differentiation of cervical epithelial cells. HNE1 affects ezrin expression in cervical intraepithelial neoplasms caused by HPV infection. When NHE1 levels are increased by EGF action, NHE1 per se, and Na+/H+ exchange, facilitate cancer cell invasion. EGF colocalizes with NHE1 in such cells. Six-1, a member of the six-gene family, regulates the cell cycle. Ezrin is associated with breast cancer metastasis, and six-1 increases the extent of such metastasis. However, although ezrin colocalizes with six-1, the expression levels are very low in normal cervical squamous epithelium. No correlation was evident between tumor size, on the one hand, and the levels of mRNAs encoding six-1 and ezrin, on the other, although the mRNA levels were higher than those of the negative control. Western blotting yielded similar data: six-1 and ezrin were expressed in cervical intraepithelial neoplastic tissue, and more highly in uterine cervix cancer tissue, particularly at later stages of disease. Thus, six-1 affects ezrin levels, indirectly triggering uterine cervix cancer development. Normally, ezrin does not have any effect on the cervix but, if cancer develops, ezrin promotes the cancer. Increases in the levels of six-1 and MHE1 enhance ezrin levels. E-cadherin and beta-catenin indirectly affect cancer development after increased ezrin levels weaken cell-cell bonds.

3. Ezrin and the endometrium

The uterine endometrium is a mucous membrane lining the inner wall of the uterus and consists of polarized luminal epithelial cells: the actin cytoskeleton facilitates cell-cell interaction. If cell polarity becomes dysregulated (as in endometriosis), a number of problems including pain, irregular hemorrhaging, and infertility may arise. Ezrin interacts with the actin cytoskeleton, and is present at higher levels in uterine endometrioid adenocarcinomas (UECs) than normal tissue. Endometrial hyperplasia is a precursor of invasive UEC cancer: ezrin is expressed in hyperplastic tissue. Invasive cancer progressed more frequently from atypical than simple or complex endometrial hyperplasia. Ezrin was predominantly present at the cytoplasmic boundaries and in cellular extensions, with some in the membranes of cells at an early stage of osteosarcoma cell metastasis. Thus, ezrin translocation from the cytoplasm to the membrane increased the metastatic potential. Surface microvilli and cellular extensions play key roles in tumor invasion. The binding site of full-length ezrin is held in an inactive state, masked by interaction between the C-terminal and N-terminal domains of the protein: phosphor-
ylation triggered by growth factors changes the oligomeric structure of cell surface molecules involved in cell–cell interactions, in turn affecting the progression of endometrial hyperplasia and uterine endometrioid adenocarcinoma. During pregnancy, endometrial ezrin expression decreases. When the three-dimensional pattern of ezrin distribution in the bovine endometrium was studied, inactive cytosolic ezrin became translocated to the apical plasma membrane, and ezrin levels fell in the cytosol and lateral cell regions. The actin-binding proteins α-actinin and talin were co-expressed with ezrin in endometriosis tissue and endometrioid carcinomas, suggesting that the proteins are co-regulated. Endometrial cancer is very closely associated with these two conditions. Ezrin was highly expressed in the basal lamina, in the effective absence of α-actinin and talin. Such absence identifies abnormal cells within normal tissue, as opposed to endometriosis and endometrioid carcinomas. In addition, ezrin is strongly expressed by certain cell types, particularly those with adhesion functions, cancer cells, the cells of endometriosis, hyperplastic cells, and the cells of lesions. Thus, precancerous conditions can develop to cancer. Ezrin contributes to the development of endometrial and other cancers.

4. Future directions
The relevance of ezrin in breast, uterine, and ovarian cancers; and uterine leiomyoma, requires further research. The physiological significance of ezrin expression is unclear: the protein affects several biological processes. Ezrin overexpression destroys the tight junctions, increasing the probability of cervical cancer, because HPV infection is thus facilitated. Also, HPV infection increases ezrin overexpression. Common factors influencing ezrin expression need to be identified: ezrin is involved in the development of cervical and endometrial cancer, and similar diseases. Mechanistic details are lacking. Work at the molecular level is required. Furthermore, ezrin may serve as a diagnostic marker predicting the development of cervical and endometrial cancer.

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Peer Reviewer’s Commentary

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and endometrial cancer, and similar diseases. Mechanistic details are lacking. Work at the molecular level is required. Furthermore, ezrin may serve as a diagnostic marker predicting the development of cervical and endometrial cancer.

In this review, the authors emphasized on the importance of HPV Vaccination. And it is very impressive that HPV infection increase ezrin overexpression. According to this Review article, HPV Vaccination is highly recommended.

(Editorial Board)