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The Expression of β-Catenin in the Epithelial Cells and Stromal Cells of Endometriosis and normal endometrial cells

Masaka Kanza Rosette

Department of obstetrics and gynecology of union hospital tongji medical college, wuhan-hubei province, China

Abstract

Endometriosis is a common benign disease defined by the presence of the endometrial epithelial and stromal cells outside of the uterine cavity. To date, the etiology, pathogenesis and path-physiology are not fully clarified. The understanding of the cellular and molecular mechanisms of pathogenesis of endometriosis is crucial in novel strategic therapeutic approaches for the endometriosis. The purpose of the present study was to examine the expression pattern, the intensity and the sub localization of β-catenin in both ectopic and eutopic endometrial cells during the proliferative phase of the menstrual cycle. A total number of 41 tissue samples were included in this study, where endometriotic tissue samples (n=26） and normal endometrial tissue samples (n=15) were investigated using immunohistochemistry（IHC）method to detect the expression patterns of β-catenin. While, the Immunoperoxidase staining technique and semi-quantitative scoring system were used to quantify the results and the comparisons between endometriotic tissues and normal endometrial tissues were also performed. Compared with normal endometrial tissues, our study found a decreased β-catenin expression in endometriotic tissues. Both, Endometriotic tissues of the ovary from non-pregnant and the peritoneum showed a statistically significant reduced-β-catenin expression ($P < 0.001$) when compared with the normal endometrial cell ($P < 0.05$). Besides the Different expression modes of β-catenin in ectopic and eutopic endometrial cells was also been detected. In conclusion the down-expression of β-catenin may have an essential role in the invasion, proliferation and differentiation of endometriosis. The alteration of expression of β-catenin may take part in the pathogenesis of endometriosis.

Keywords: β-Catenin, Endometriosis, Normal endometrial cells, Epithelial cells, Stromal cells

1. Introduction

Endometriosis is a common gynecological benign disease. It is characterized by the presence of endometrial cells outside the uterine cavity (1, 2, 3, 4). The cause of endometriosis remains unknown and it is still an enigmatic disease.

Endometriosis is a condition that is due to the migration and proliferation of endometrial cells outside the uterine cavity, which led to injury more or less deep. The hormonal functions, reproductive functions and often digestive functions are seriously affected (5, 6, 7, 8).

*Corresponding Address: Masaka Kanza Rosette Department of obstetrics and gynecology of union hospital tongji medical college, wuhan-hubei province, China. Email: issabeck07@yahoo.fr

The main locations are the peritoneal cavity (including ovaries, uterine ligaments, the peritoneum, cul–de-sac and retrovaginal septum) and the extra-peritoneal lesions also are reported. It can also reach to the different locations in the Digestive tract, whence there are many types of endometriosis. It affects 1-10% of women in the reproductive age and, it is also found in 30-40% of women with fertility problem and 80% of women with chronic pelvic pain (5, 9, 10). Nevertheless, endometriosis may also affect women younger than 20 years old. They generally present with chronic pelvic pain, dyspareunia, dysmenorrhea and infertility (6, 11, 12). The risks factors, which are likely related to increased menace exposure to menstruation, include age, short menstrual cycle, long duration of menstrual

flow, null parity and positive family history of endometriosis (13, 14, 15).

β-catenin signaling pathway has demonstrated that it is essential for several biological processes like proliferation, differentiation, and regulation of the cell cycle to be present and also it plays a critical role in the pathogenesis of various diseases. This protein assumes a dual function of the coordination of cell adhesion and gene transcription. It plays an important role in sticking cells together and in communication between cells. In this pathway, certain proteins are attached to β-catenin, which triggers a multi-step process allowing the protein to move into the nucleus (13, 15, 16). In the nucleus, β-catenin interacts with other proteins to control the activity or the expression of particular genes. The Wnt/β-catenin is required for several biological processes such as proliferation, differentiation and cell cycle regulation, and it has a crucial role in the pathogenesis of various diseases, including cancer.

In the uterine, at the menstrual cycle in proliferative phase, the estrogens induce Wnt/β-catenin signaling. In the secretory phase of the normal menstrual cycle, yet, progestagens offset estrogen-induced proliferation by inhibition of Wnt/β-catenin signaling, consequently inducing differentiation (16, 17). Another study also observed that, the clear nuclear localization of β-catenin in the proliferative phase of the menstrual cycle had high level of estrogen level and unopposed by progestagens. In the secretory phase of the menstrual cycle (when there are progesterone and estrogen increase), the nuclear β-catenin accretion is decreased (18).

Progesterone neutralizes the proliferative effects of estrogen in the menstrual cycle by obstructing estrogen-induced Wnt/β-catenin signaling. Those data suggest that progesterone neutralizes the proliferative effects of Estrogen in the normal menstrual cycle by inhibiting Wnt/β-catenin signaling.

In accordance with those elements, estrogen and progesterone may modulate Wnt/β-catenin signaling in normal endometrium to preserve the equipoise between proliferation and differentiation (19).

In endometriosis, β-catenin signaling was located at the development of the disease. In the literature, the signaling of progesterone causes the significant increase in expression of Wnt7a. Wnt7a will induce the expression of HOXA10 gene which is involved in the development of endometriosis (2, 4, 19).

2. Material and Methods

2.1. Patients and Specimens

This research was performed on tissue samples from patients aged 20-44 years who underwent laparoscopy for endometriosis. Normal endometrial cells in the proliferative phase as a control cases (25-45 years) included patients who had undergone hysterectomies for myoma.

The histological diagnosis of endometriosis was conducted at the gynecology department of union hospital of tongji medical college, Huazhong University of science and technology (HUST) between November 2012 to September 2013.

All tissue samples were obtained with full and informed consent from the patient. Endometriotic cyst of the ovary from non-pregnant （n=10), scar endometriosis (n=3), endometriosis of the peritoneum (n=8), endometriosis of the cervix (n=2), ovary cyst endometriosis from women who were pregnant (n=3) and for the control patient group of normal endometrial cells in the proliferative phase (n=15).

2.2. Immunohistochemistry staining

All tissues collected were fixed in formalin, frozen at 4℃ and were embedded to paraffin for the IHC staining. The samples were performed on 3mm sections of paraffin embedded. Slides were heated at 60 ℃ ovens for 2hours**,** rinsing of specimens in xylene for 10 minutes, rehydrated through alcohols rinsing with PBS for 5 minutes, 3 times each. The slides were put into 3% solution of endogenous peroxidase activity in absolute ethanol for 20 minutes.

The slides were placed in the standard microwave and incubate with high-temperature antigen retrieval for 3 minutes followed by a 3 minutes cool down. The slides were washed with PBS 3 times. 5minutes each.PBS was used to wash the slides 3 times 5 min each followed by application of 5% BSA on the slides, left to dry for 15 minutes.

Primary antibody (rabbit polyclonal IgG, Beijing) 50μl diluted was put on each slide and kept at 4 ℃ overnight. PBS was then used to wash the slides 3 times 5 min each and excess PBS was wiped from the slides.

50μl of corresponding secondary antibody was put on the slides and the species kept at 4 ℃, incubated for 50min. PBS was used to wash the slides three times, each time 5min.

Removing the PBS solution was done and each slide was treated with 75μl freshly prepared DAB solution.

Monitored on microscope for control color. When the color was complete, tap water, counterstained with hematoxylin was applied to the slides followed by 1% hydrochloric acid, ethanol differentiation for 2

seconds, tap water**,** and slicing through graded alcohol series (70-100%) 10min a gradient. Dehydration in xylene was done and Drizzle paramount coverslip onto slides and let to dry overnight.

2.3. Analysis of immunohistochemistry

Each section was immunostained, analyzed semi-quantitatively using a modified version of Quick Score method with a magnification of x400 and the intensity of cell staining was scored as 0, 1, 2 or 3 corresponding to the presence of a negative staining, low staining, moderate staining and high staining, respectively. The percentage of positive cells for each staining intensity (1 is 0–25%; 2 is ≥25–50%; 3 is ≥50–75%; 4 is≥ 75–100%). The total number of cells in each field and the number of stained cells were counted graded in intensity.

The average increase was positive percentage, as follows: (% of stained cells of the intensity category 0x1) = 0, (% of cells stained at intensity grade 1 x 2) = 2, (% of stained cells to the category of intensity 2 x 1) = 2 (% of stained cells to the intensity class 3 x 2) = 6. Then the results obtained were adding, 0 + 2 + 2 +6 = 10. Thus the results obtained was between 0 and 12 where 12 was obtained was 100% of cells stained strongly (3 +) (20).

2.4. Statistical Analysis

We used analysis of variance (ANOVA) with SPSS 17, 0 for statistical study for the analysis of all data. Analysis of variance was used to examine the expression of β-catenin on each type of epithelial and stromal cells for each of endometriosis tissue and normal endometrial cells in the proliferative phase. The statistically significant trend for this study was considered as p-value <0.05.

3. Results

Immunohistochemistry staining performed on endometriotic tissues and the normal endometrial cell in the proliferative phase revealed a decreased expression of β-catenin in endometriotic tissues compared with normal endometrial tissues and the staining were more intense in the epithelial cells than in the stromal cells.

Analyzing statistically our results on β-catenin expression pattern in the endometriotic tissues of the ovary in non-pregnant women and in peritoneal endometriotic tissues, we found significant reduced β-catenin expression, (P-value <0,001) in epithelial and stromal cells of endometriotic tissues of the ovary from non-pregnant women and endometriotic tissues of the peritoneal compared with the epithelial and stromal cells of normal endometrial cell in the proliferative phase (P-value <0, 05). But endometriotic tissues of the ovary from non-pregnant women were lower β-catenin expression in both epithelial and stromal cells compared with epithelial and stromal cells endometriotic tissues of the peritoneum, with no significant difference between them (figure 2). In the other hand we also found a very lower β-catenin expression in endometriotic tissues of the ovary from the pregnant women and endometriotic tissues for the scar than in other types of endometriotic tissues. Endometriotic tissues of the ovary from the pregnant women were not only lower but very weak also compared with scar and others types of endometriotic tissues. Besides that, endometriotic tissue of the Cervix, a positive and strong β-catenin expression was found in both epithelial cells and in the stromal cells compared with normal endometrial cells and others types of endometriotic tissues.

The sub localization, in the epithelium of normal endometrial cells, a positive β-catenin staining was found in the plasma membrane and cytoplasm but stained negative in the nucleus. For the stromal cells, positive expression of β-catenin was noted in the plasma membrane and cytoplasm and nucleus.

In ovarian endometriosis, the plasma membrane, the cytoplasm and the nucleus of epithelial cell stained positive for β-catenin. Stromal cells had positive expression in the plasma membrane and in the cytoplasm except for the nuclei. Peritoneal endometriosis stained positive for β-catenin in the plasma membrane and cytoplasm except in the nucleus of epithelial cell.

For the stromal cell, only the plasma membrane was positive for β-catenin. Endometriosis of ovary from the pregnancy had positive expression of β-catenin only in the plasma membrane of epithelial and stromal cells, but scar endometriosis had positive only in the plasma membrane of the epithelial cells, stromal cells stained negative. Cervix endometriosis had positive results in all in both epithelial cells and stromal cells. Whereas the nuclei of the stromal cells were only the negative β-catenin expression. All the results of our immunohistochemistry staining are shown below in the figure 1 and table 1.

4. Discussion

We used immunohistochemistry method to examine the expression of β-catenin in endometriotic tissues and normal endometrial cells. The intensity was found in sub localization in this study such as plasma membrane, cytoplasm and nuclei in endometriotic tissues and in normal

endometrial tissues. Our results agree with those of some authors and refute also another.

Thus, it seems that altered β-catenin expression have a role in the pathogenesis of endometriosis. B-catenin is a protein which plays a key role as a major component of adherent junctions.

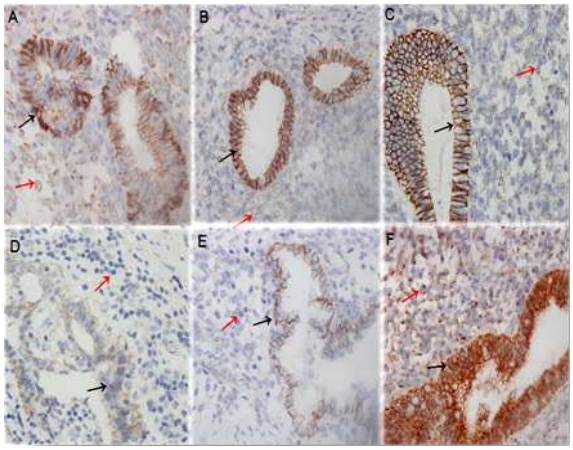

Figure 1. β-catenin immunostaining in representative immunohistochemistry tissue. (A) the normal endometrial cell in the proliferative phase. (B) Endometriotic tissues of Ovarian from non-pregnant. (C) Endometriotic tissues of peritoneal. (D) Endometriotic tissues of Ovarian from pregnant women. (E) Endometriotic tissues of the scar. (F) Endometriotic tissues of the cervix. Cell Original magnification x400.

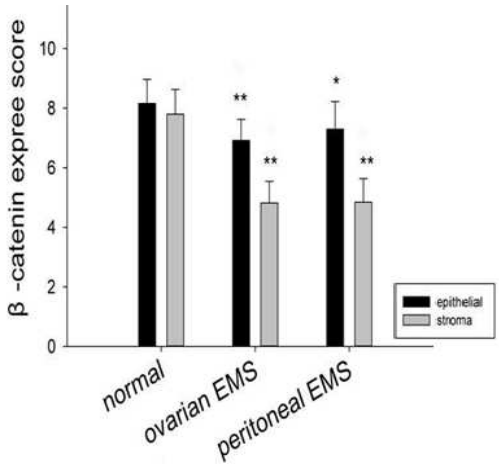

Figure 2. Each bar represents the mean phase of β-catenin expression in normal endometrial cells in proliferative cells (* P-value <0, 05) and in endometriotic tissues (** P-value <0,001).

Table1. β-catenin expression sub location in epithelial cells and stromal cells in endometriosis and normal endometrial cells. (+) = positive β-catenin staining; (-) = negative β-catenin staining; (++) = positive and strong β-catenin staining.

Types	Groups	Plasma Membrane	Cytoplasm	Nucleus
Epithelial cells	Normal endometrial cells	+	+	-
	Ovary endometriosis from non-pregnant	+	+	+
	Peritoneal endometriosis	+	+	-
	Scar endometriosis	+	-	-
	Ovary endometriosis from pregnant	+	-	-
	Cervix endometriosis	++	++	++
Stromal cells	Normal endometrial cells	+	+	+
	Ovary endometriosis from non-pregnant	+	+	-
	Peritoneal endometriosis	+	-	-
	Scar endometriosis	-	-	-
	Ovary endometriosis from pregnant	-	-	-
	Cervix endometriosis	+	+	-

It seems that tight control of wnt/ β-catenin signaling in time and space is important for initiation, development and normal function of the female reproduction tract. However if wnt/ β-catenin signaling is not kept in check, it easily seems to initiate or contribute to development of a number of uterine disorders. In this study, we hypothesized that the decreased expression of β-catenin may influence the pathogenesis of endometriosis, while contributing to its invasive nature (15, 16, 21, 22). In endometriotic tissues of the ovary from non-pregnant women, our study found the expression of β-catenin in both epithelial and stromal cells. A statistical significant reduced β-catenin expression (P-value <0,001) was found compared with the normal endometrial cells (P- value <0, 05). About the sub localization of this type of endometriosis, we saw a positive staining in the plasma membrane, cytoplasm and the nucleus of epithelial cells. However, there was a diffuse positive expression of β-catenin in stromal cells except in the nucleus. Our results correspond with those found by Ruthy et al, where they reported a decreased β-catenin expression in endometriotic cells compared with normal endometrial cells. Besides, in endometriotic tissues, β-catenin expression was positive only in epithelial cells but, no immunoactivity of β-catenin in stromal cells was observed. More other, they observed positive β-catenin staining in both, epithelial and stromal cells in normal proliferative endometrial cells (23).

For peritoneal endometriosis, we found the expression of β-catenin expression in both epithelial and stromal cells. Additionally a statistically significant decreased (P-value <0,001) β-catenin expression in endometriosis compared with the normal endometrial cells (P-value <0, 05) was detected. β-catenin staining was positive in the plasma membrane and cytoplasm and negative in the nucleus of epithelial cell. Whereas, the positive β-catenin staining was seen only in the plasma membrane of the stromal cells.

. S.scotti et al had a similar result as ours which demonstrated that β-catenin expression was only detected at the apical portions of the lateral membranes of the glandular epithelium. But no obvious immunostaining for β-catenin was detected in the nuclei of epithelial cells of ectopic endometria. While, they did not display data about stromal cells (24).

A lower β-catenin expression was found in endometriotic tissues of the ovary from the pregnant women and endometriotic tissues of the scar than in the endometriotic tissues of the ovary from non-pregnant women, peritoneum and cervix. In endometriotic tissues of the ovary from the pregnant women, β-catenin expression was positive in the plasma membrane of the epithelial and the stomal cells. In the literature, we found no publication which reported β-catenin expression in ovarian endometriosis of the pregnant woman.

It has been reported by different studies, that Wnt/ β-catenin play an important role in the proliferation and differentiation in the physiology of the normal uterus, and β-catenin has an essential function in the development of the embryo; in the implantation of blastocyst, decidualization of endometrium and in the formation of the placenta (25, 26, 27).

Receptivity of endometrium for implantation depends highly on correct hormonal signaling towards the moment of implantation. A study of Hayashi et al. on the expression of different wnt receptors, and their receptors were found in the site of implantation in pregnant mice. At day 5, after fertilization, the wnt/ β-catenin signaling pathway was activated in specific endometrial regions in the vicinity of a blastocyst, indicating cross-talk between blastocyst and the endometrium. This situation was confirmed using pseudopregnant mice which received an injection of wnt7a and a profound activation of wnt/ β-catenin signaling was observed throughout the exposed region. Also, the authors showed that when mice blastocysts were treated with the wnt/ β-catenin signaling inhibitor Sfrp2 or when high amounts of Sfrp2 were present during implantation, the implantation rate dropped by approximately 50%. These investigations indicated that in the mices, embyo-induced wnt/β-catenin signaling at the site of blastocysts attachment is prerequisiste forsuccessful implantation.

About decidualization, tudy had suggested that all ligands and receptors were found in the site of implantation in pregnancy in mice. Progesterone was revealed to be responsible for Bmp2 mediated Decidualization. Wnt4 acts downstream from Bmp2 and wnt4 conditional knockdown in mice was shown to affect stromal cell survival, differentiation and responsiveness to progestagens (12, 27). According to another study, the expression of Progesterone receptor was indispensable for the nuclear translocation of β-catenin in combination with wnt4 which is a key regulator of progesterone signaling during embyo implantation and decidualization, and also in the development of the uterus after normal delivery. Progesterone signaling and β-catenin work in series resulting in theactivation of another pathway via the progesterone receptor (15, 18, 19). Results suggest that β-catenin is directly in the centre of

progesterone-dependent mesenchymal-to-epithelial signaling during the initiation of maternal-embryo interaction and also help the stromal compartment, via activation of β-catenin to mediate someof the actions of progesterone on the epithelium (16, 27, 28). According to these observations, we guess that β-catenin is expressed differently in pregnant women without endometriosis and in pregnant women with endometriosis.

Scar endometriosis was positive only in plasma membrane of epithelial cells. The staining was negative for β-catenin expression in the stromal cells. One study investigated on β-catenin and scar endometriosis but they did not publish the result of their work (29).

Generally, endometriosis of the cervix is asymptomatic and is often discovered incidentally during histological examination. Endometriosis of the cervix is one type of endometriosis and is located in a rare site as compared to other types of pelvic genital endometriosis. Because of the path of constant ejection of menstrual blood, the cervix has a chance to be implanted by the endometrial debris and develop ectopic lesion, Sampson's menstrual reflux and implantation theory or during trauma on the cervix, such as biopsy, conization, cauterization and/or curettage, which may also explain the presence of endometriosis in the cervix (3, 26).

Interestingly, compared with the other types of endometriosis and the normal endometrial cells, the cervical endometriosis had the strongest β-catenin expression both in the epithelial and stromal cells. And the nuclei of the stromal cells were the only colorless. The study of β-catenin expression in cervix endometriosis is not reported in literature. Supplementary study is needed in β-catenin expression and endometriosis of the cervix.

Our result on the expression of β-catenin implies that different alteration in the β-catenin expressions could contribute to the pathogenesisof endometriosis. It seems logical that different changes in epithelial adhesion molecules participate in the initiation and/or disease progression of a benign as opposed to a malignant disease. Additionally, the changes of β-catenin expression are dissimilar in different types of endometriosis, an interesting finding is that endometriosis disease has different biological behaviors according to its localization and intensity.

5. Conclusion

The objective of this present study was to examine the expression patterns of β-catenin between the endometriotic cells and in the normal endometrial cells in proliferative phase.

The finding is that β-catenin was down-regulated in endometriotic cells as compared to normal endometrial cells in the proliferative phase. The differences of β-catenin expression in the epithelial and stromal cells and the intensity within the various types of endometriosis, such as, more frequent high membrane plasma and cytoplasmic expression in endometriotic tissues of the cervix, and lower β-catenin expression in endometriotic tissues of the ovary from the pregnant and endometriotic tissue of the scar, as well as the differences in epithelial and stromal β-catenin expression patterns are a motivating finding in view of a disease which is able of invasion and metastasis.

Finally, the detection of β-catenin expression may provide novel therapeutic treatment options for endometriosis except for cervix endometriosis where β-catenin expression is significantly high compared to the control cases. Further β-catenin studies should be necessary to investigate the expression patterns in the various types of endometriosis.

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