Expression of the Laminin-5 γ 2 Chain Is Associated With Acquisition of Malignant Traits in Ovarian Serous and Mucinous Tumors.

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Abstract

Background

Ovarian tumors are predominantly of epithelial origin and are currently divided into three groups: Adenoma, borderline tumor, and adenocarcinoma by the presence or absence of invasion and cellular atypia. However, it is difficult to assess invasion, so a more objective biomarker would be desirable. Laminin-5 (Lam5) is a protein that constitutes the extracellular matrix of the basement membrane, and it is composed of three short-chain subunits. One of them, the Lam5 γ 2 chain (Lam5 γ 2), has been reported to be expressed in some malignant tumors and is suggested to be related to tumor cell invasion. Against this background, we investigated immunohistologically whether the Lam5 γ 2 would be useful as a marker to predict invasion in ovarian serous and mucinous tumors.

Methods

Immunohistochemistry for Lam5 γ 2 was performed on a total of 80 cases of serous and mucinous tumor adenomas, borderline tumors, and adenocarcinomas, and the differences in the localization of Lam5 γ 2 expression were observed.

Results

The basement membrane expression of Lam5 γ 2 tended to be preserved or had disappeared in half of the adenomas and borderline serous tumors. In all cases of adenocarcinoma, the expression on the basement membrane had disappeared. The frequency of expression in tumor cells increased in the order of adenoma, borderline tumor, adenocarcinoma. In particular, in most adenocarcinoma cases a cytoplasmic expression was observed. The same tendency was noted in mucinous tumors, and the basement membrane expression tended to disappear in the order of adenoma, borderline tumor and adenocarcinoma. Many cases of adenocarcinoma were observed among the tumor cells. In adenocarcinoma cases of both types of tumor, many tumor cells showed prominent cytoplasmic expression particularly in the microinvasive foci and in the invasive front.

Conclusions

The disappearance of Lam5 γ 2 from the basement membrane and its aberrant expression in serous and mucinous tumor cells may serve as a phenotype for invasiveness.

Background

In general, the prognosis for ovarian adenoma tumor patients is good, but it is one of the worst for other organ adenocarcinoma malignancies. According to the World Health Organization classification, there are 14 types of tissue subtypes classified as ovarian tumors, of which epithelial tumors account for 90% of the total [1]. Epithelial tumors are further divided into five categories: Serous, mucinous, endometrioid, clear cell, and Brenner tumors [2]. The former two subtypes were thought to be derived from the

superficial epithelium of the ovary, but some of the serous adenocarcinomas have recently been reconsidered as derived from the tubal epithelium [3]. Each of these ovarian tumors is histopathologically divided into three groups: Adenoma, borderline tumors, and adenocarcinoma, which are closely correlated with clinical findings and, especially, patient prognosis [2]. From this point, the histopathological diagnosis of benign or malignant ovarian tumors leads to the estimation of patient prognosis and plays an important role in deciding the treatment course. These three groups of tumors are currently diagnosed based on the degree of cellular atypia and the presence or absence of tumor cell invasion into the stroma. If invasion is observed, the case is undoubtedly diagnosed as a carcinoma. Borderline tumors are diagnosed when there is no invasion, but the cells are atypical and proliferative. However, although it is important to evaluate whether the tumor has invaded into the stroma, it is a fact that there are many cases in which it is difficult to evaluate invasiveness, and low reproducibility is also a major problem [4, 5].

Laminin-5 (Lam5) is one of the proteins that make up the extracellular matrix, and it is mainly located along the basement membrane in normal tissues [6]. The essential function of Lam5 is to play an important role in adhering epithelial cells to the basement membrane, but it is also involved in cell migration, which is one of the wound healing mechanisms at injured sites, such as ulceration [7, 8]. It also regulates some cell functions by interacting with cell surface receptors [9]. Lam5 consists of three short-chain subunits, α , β , and γ [9–13], which consist of $\alpha 3$, $\beta 3$, and $\gamma 2$ chains, respectively [10–14]. Among them, the Lam5 $\gamma 2$ chain (Lam5 $\gamma 2$) has been reported to show abnormal expression during the tumor developmental process of various malignant neoplasms [11, 15–20]. In particular, it has been reported, that it is highly expressed in the advanced invasion of tumor cells [16, 18, 19]. Thus, it has been suggested that the Lam5 $\gamma 2$ is deeply involved in the invasion of tumor cells in several organs.

In this study, we investigated immunohistochemically whether the expression of Lam5 $\gamma 2$ may serve as a biomarker for invasion ability of epithelial ovarian tumors.

In this immunohistochemical study we investigated the expression of Lam5 $\gamma 2$ and evaluated its utility as a biomarker for invasion ability of epithelial ovarian tumors.

Methods

Case selection

Stored case samples obtained from the archives of the Diagnostic Pathological Division, University of Toyama Hospital between January 2005 and December 2014 were examined. Because these cases were preoperatively suspected of being ovarian tumors, tumor resection had been performed and then pathologically diagnosed as serous or mucinous tumors. Specimens were stored as 10% buffered formalin-fixed paraffin-embedded sections. The patients comprised 80 Japanese women with ages at the time of diagnosis ranging from 18 years to 80 years (mean, 47 years). These specimens were routinely stained with hematoxylin-eosin stain, then histopathologically divided into serous or mucinous tumor groups, and then finally diagnosed as adenomas, borderline tumors, or adenocarcinomas. Among the

serous tumors, there were 15 cases of adenomas, 14 cases of borderline tumors, and 12 cases of adenocarcinomas. On the other hand, among the mucinous tumors, there were 13 cases of adenomas, 16 cases of borderline tumors, and 10 cases of adenocarcinomas. Pathological slides obtained from all cases were reviewed by two experienced senior pathologists (JI and AN), who were blinded to the clinical data, for confirmation of the pathological diagnoses.

Immunohistochemistry

Immunoperoxidase reactions were performed with an enzyme treatment method using BenchMark GX[®] automated IHC/ISH slide staining system (Roche), according to the manufacturer's instructions. All reacted sections were reviewed by two investigators (YT and JI) who assessed the immunoreactivity. In initial disagreement cases, the discrepant cases were reviewed together via a double-headed microscope, and a consensus was reached. The evaluation of immunoreactivity for anti-Laminin5 γ 2 chain mouse monoclonal antibody (clone D4B5 MILLIPORE, x500 dilution) was based on the staining pattern in the basement membrane or the cytoplasm of tumor cells. The immunohistochemical result was regarded as negative if <5 % of the tumor cells were immunoreactive. Immunohistochemical evaluations were performed independently by two investigators, and the yielded results were considered similar according to Cohen's kappa coefficient ($\kappa^2 > 0.98$).

Statistical analysis

Statistical analysis was conducted using StatFlex ver. 6 (Arteck Co. Japan). Significant differences were determined by comparing the positive or negative results for Lam5 γ 2 chain expression in adenomas, borderline tumors, and adenocarcinomas of serous and mucinous tumors. Using the contingency table analysis, $p < 0.05$ was set as a significant difference by the χ^2 test.

Results

Serous tumors

In serous tumors, linear Lam5 γ 2 expression was observed along the basement membrane in 7 of 15 adenomas (47%), while it was also expressed in the cytoplasm of tumor cells in 1 case (7%). Six cases (40%) retained basement membrane expression and were not observed cytoplasmically (Fig. 1a). In borderline tumors, 7 of 14 cases (50%) showed the linear basement membrane expression, but the expression on the basement membrane had completely disappeared (Fig. 1b) in 7 cases (50%). The cytoplasmic expression in tumor cells was observed (Fig.1c) in 10 cases (71%). Only one case (7%) retained basement membrane expression without cytoplasmic expression, but 4 cases (29%) had lost basement membrane expression and retained cytoplasmic expression. The basement membrane expression was completely lost in all serous adenocarcinoma cases, and the cytoplasmic expression of invaded tumor cells was observed in 11 of 12 cases (92%). Moreover, there was a tendency for the solitary invading tumor cells that had lost their mutual adhesion, such as in the invasive front, to be strongly expressed especially in the cytoplasm (Fig. 1d).

Mucinous tumors

In mucinous tumors, 10 of 13 (77%) adenoma cases had preserved expression along the basement membrane (Fig. 2a). Only 3 cases (23%) revealed cytoplasmic expression with preserved basement membrane expression. On the other hand, 3 cases showed cytoplasmic expression without basement membrane expression. In borderline tumors, 9 of 16 (56%) cases showed expression in the basement membrane, of which 7 cases (44%) did not show cytoplasmic expression (Fig. 2b). There were also 2 cases (13%) in which the basement membrane expression was preserved and the cytoplasmic expression was shown. In addition, 5 cases (31%) showed neither basement membrane nor cytoplasmic expression (Fig 2c). In the mucinous adenocarcinomas, Lam5 γ 2 was diffusely expressed in the cytoplasm (Fig. 2d) of tumor cells in 6 of 10 cases (60%). The basement membrane expression had disappeared in all of these cases. A list of immunohistochemical study results is shown in Table 1. Both serous and mucinous tumors revealed a tendency to show decreased expression of Lam5 γ 2 along the basement membrane and increased cytoplasmic expression in the order of adenoma, borderline tumors, and adenocarcinoma. There was a statistically significant difference in expression patterns between adenomas, borderline tumors, and adenocarcinomas of serous and mucinous tumors at $p < 0.05$.

Discussion

Ovarian tumors show a variety of histological subtypes, most of which are epithelial tumors. These epithelial tumors have been classified into five categories: Serous, mucinous, endometrial, clear cell, and Brenner tumors. Furthermore, they have been divided into benign tumors, borderline tumors, and adenocarcinomas in order to estimate the prognosis of patients. Benign and borderline tumors are extremely rare among endometrial, clear cell and Brenner tumors, and serous and mucinous tumors are most often encountered [2]. It is important to correctly distinguish between benign tumors, borderline tumors, and adenocarcinomas among the serous and mucinous tumors not only for patient outcome but also for the selection of treatment. In fact, these three types of tumor are diagnosed by the presence or absence of cellular and histological atypia, invasion, or metastasis. In particular, the borderline tumors are not present in the histological subclassification of tumors in other organs; they have been recognized as being neither adenomas nor adenocarcinomas. This type of tumor is positioned as an intermediate lesion while leaving the possibility of malignancy open when there are only a few atypical cells present or when the invasion, an important factor, cannot be confirmed. However, an objective evaluation of atypia is not always easy, and it is often also difficult to assess the presence of invasion and its risk. Therefore, in this report, we conducted immunohistochemical studies on the Lam5 γ 2 in order to search for biological markers that might be useful in an objective method to evaluate tumor cell invasiveness.

Laminins are a group of molecules comprising more than 16 isoforms that compose the basement membrane. Their functions are diverse, among them is involvement in cell differentiation, cell adhesion, migration and structural maintenance of cells [10, 12]. Lam5 is composed of three short-chain subunits, α , β , and γ that consists of α 3, β 3, and γ 2 chains, respectively [10–14]. It was recognized as a ligand for urinary-type plasminogen activator receptor, uPAR, in previous studies but has recently also been used as

a marker for tumor cell invasion in some human malignancies [21–25]. Among these three subunits, the Lam5γ2 has been reported to show aberrant expression during the development and progression of various malignant tumors [11, 12, 15–20]. Although the Lam5γ2 is originally located in the basement membrane of epithelial cells in normal tissues, it may show a changed expression in tumor tissue. For example, the basement membrane expression may disappear in non-invasive lesions, or it may be observed in the cytoplasm of some tumor cells. Besides, the expression tends to be concentrated in the sprouting tumor cells at the micro-invasive lesions. Furthermore, in advanced invasive lesions, this tendency becomes remarkable, and the expression has been observed in many tumor cells at the invasive front.

In this study, the patterns of Lam5γ2 expression were compared immunohistochemically in adenomas, borderline tumors, and adenocarcinomas of serous and mucinous tumors. The expression patterns among the three groups showed similar tendencies in both types of tumor. In the adenomas of both types, linear expression was observed along the basement membrane with which the tumor cells and the stroma are in contact. In the borderline tumors, some cases were observed in each type in which linear expression in the basement membrane was retained or had disappeared. There were also cases in which cytoplasmic expression was observed in some tumor cells. The basement membrane expression showed a tendency to disappear in many cases of adenocarcinoma. Among the cases of adenocarcinomas, the microinvasive lesions showed cytoplasmic expression consistent with the suggestion that the tumor cells were sprouting into the stroma. In advanced cases that invaded extensively, the cytoplasmic expression was observed predominantly in tumor cells at the invasive front. Therefore, as the malignancy gradually increased in adenomas, borderline tumors, and adenocarcinomas, there was a tendency for the basement membrane expression to disappear and for an increased aberrant cytoplasmic expression. These findings suggest that invasiveness should be regarded as one of the malignant phenotypes of tumor cells, both serous and mucinous. It is possible that this malignant trait was acquired by intracellular expression of the Lam5γ2. A similar trend has been observed in other organs. In uterine cervical adenocarcinoma, a gynecological malignancy similar to that in the present study, the cytoplasmic expression of Lam5γ2 chain was observed as the stage of the disease increased from intraepithelial carcinoma through microinvasive carcinoma to invasive carcinoma [24]. A previous report about Paget's disease showed a similar tendency between non-invasive and invasive cases, similar to the present study [25].

So why is the Lam5γ2, which is originally a component of the basement membrane, expressed in the cytoplasm of the tumor cell itself? To date, no definitive data has been established to clarify this observation. It has been suggested that the displacement is the result of abnormalities in the transcriptional mechanism of the Lam5γ2 chain during the development of tumor cells, and various signal transduction abnormalities have been reported. Beta-catenin may be inducing gene expression of the Lam5γ2 in the invasive front of the tumor cells and in the area that shows highly dispersed invasion. Increased Lam5γ2 is secreted extracellularly and is cleaved by the membrane-type matrix metalloproteinase (MT1-MMP) on the cell surface. The cleaving releases a fragment containing an epidermal growth factor (EGF)-like sequence. It is considered that these fragments regulate the autonomous autocrine mechanisms to induce tumor cell proliferation and migration by binding to EGF

receptors on the cell surface of tumor cells [9]. We suggest that a similar mechanism may be occurring in ovarian tumors as well as in the present study. In future studies, it is necessary to study whether knockdown by β -catenin siRNA suppresses the expression of the Lam5 γ 2, or whether the expression of the Lam5 γ 2 was enhanced by β -catenin activation.

Conclusions

In summary, our study revealed that as epithelial serous or mucinous tumors of the ovary gradually increase their malignant traits ranging from adenocarcinoma, borderline tumors to adenocarcinomas, Lam5 γ 2 disappears from the basal membrane and appears in the cytoplasm of the tumor cells. These two phenomena may indicate that Lam5 γ 2 is useful as a good biomarker for predicting invasion, which is a malignant trait in ovarian serous and mucinous tumors.

Abbreviations

Lam5

Laminin-5; Lam5 γ 2:Laminin-5 γ 2 chain

Declarations

Authors' contributions

YT and JI contributed to protocol/project development. YT, JI, AN, TM, KT, ST, TS and AN contributed to data collection and management. YT, MO and YN performed immunohistochemical study. YT, JI and AN mainly wrote and edited the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

All data analyzed in this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study protocol was approved by the Medical Ethics Committee of Toyama University (IRB No. RIN 29-105). Records/ information of all women in the study were completely anonymized and deidentified prior to analysis. In addition, this research is a retrospective study, and we are not required to submit additional informed consent forms concerning this research by the Ethics Committee of the Institution.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no conflicts of interest.

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Immunohistochemical findings on the laminin-5γ2 chain in serous tumors of ovaries. a: adenoma, linear positive reaction showing along the basement membrane. b, c: borderline tumor, the basement membrane expression has disappeared (b), the tumor cells being cytoplasmically expressed without basement membrane expression (c). d: adenocarcinoma, the invaded tumor cells showing cytoplasmic expression.

Figure 2

Immunohistochemical findings for the laminin-5γ2 chain in the mucinous tumors of ovaries. a: adenoma, linear positive reaction showing along the basement membrane. b, c: borderline tumor, the basement membrane expression preserved (b), the basement membrane expression has completely disappeared (c). d: adenocarcinoma, the invaded tumor cells showing cytoplasmic expression.

Supplementary Files

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