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Mast Cell Infiltration and Leukotriene Receptor Expression in Malignant Gynecologic Tumors: Pathological Findings to be Common in Various Carcinogens and Characteristic Mechanisms

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Abstract

The main therapies for malignant tumors include surgery, chemotherapy, and radiotherapy. However, many patients cannot be cured with these therapies because the mechanism of development of tumors remains unknown. So, to establish effective therapeutic method, it is necessary to make these mechanisms clear. We have already identified leukotriene receptor expression and mast cells infiltration in various malignant tumors. In this time, we observed the gynecologic malignant tumors (endometrial cancer, cervical cancer and ovarian cancer) to obtain additional data. As a result, mast cells infiltration and the expression of leukotriene receptor were common in the tumor tissues of all gynecologic malignant tumors and, similar to the other malignant and benign tumors that we previously studied. These findings were common to all tumors. These malignant gynecologic tumors have different carcinogens and characteristic mechanisms. However, from these results, the pathologic findings common to all the tumor tissues, including mast cell infiltration and expression of the leukotriene receptor, were found. Thus, even in cancers that vary in terms of the process of carcinogenesis and tumor extension, the tumor can be inhibited by controlling the leukotriene receptor response. Leukotriene receptor antagonists may become a novel type of oncotherapy in the future for the treatment of various tumors.

Keywords: Mast cells; Leukotriene receptor; Endometrial cancer, Cervical cancer, Ovarian cancer

Abbreviations: cysteinyl leukotriene receptor (CysLT), G protein-coupled receptor (GPCR)

Introduction

The main therapies for malignant tumors include surgery, chemotherapy, and radiotherapy. However, many patients cannot be cured with these therapies. In many cases of benign tumors, the approach is to observe the progression of the tumor (whether it does or does not change to a malignancy). The tumor is removed surgically when necessary. Then the patients undergo a periodic health examination for early detection of the malignant tumor. Because the mechanism of development of tumors remains unknown, these approaches are meant to detect a malignant tumor early. In other words, an effective method to save patients with malignant tumors is early detection and early treatment. Our opinion, which was derived from a series of investigations about tumors, is that both malignant and benign tumors are proliferative lesions, and we showed evidence that the tumor lesion area of various malignant tumors and benign tumors is similar [1-3]. Infiltration of mast cells and expression of leukotriene receptors occurs in both types of lesions. We also reported the effects of antitumor therapy on spontaneous tumors in laboratory animals based on common pathological findings [1]. In this study, we histopathologically observed endometrial cancer, cervical cancer, and ovarian cancer, confirmed common findings that are similar to other tumors, and report additional data.

Materials and Methods

Tissue Samples

Tumor tissues were obtained from patients who were diagnosed with endometrial carcinoma (n = 16), cervical

squamous cell carcinoma (n = 18), and ovarian high-grade serous carcinoma (n = 13) that were confirmed by surgical pathology. Tumors were sampled after the patients gave their informed consent in accordance with the Helsinki Declaration.

Histopathology and Localization of Mast Cells

Tumor tissues from these patients were fixed with 10% buffered formalin, and after routine dehydration, were embedded in paraffin. Sections 5-μm thick were stained with hematoxylin and eosin (HE) and examined under a light microscope. To identify mast cells in each specimen, paraffin sections were stained with toluidine blue. The granules within mast cells contain heparin and sulfated glycosaminoglycan that stain metachromatically with toluidine blue. The 5-μm-thick tissue sections were stained for 30 min with a staining solution containing 0.05% toluidine blue O (Kanto Chemical Co., Inc., Tokyo, Japan) in a citric acid phosphate buffer (pH 2.5) and were then examined with light microscopy.

Detection of Leukotriene Receptors using Immunohistochemical Staining

Immunohistochemical staining for the cysteinyl leukotriene receptor (CysLT) 1 and 2 was performed to detect the expression of leukotriene receptors in the tumors under a light microscope. The 5-μm-thick tissue sections were immunohistochemically stained using the streptavidin-biotin method (Histofine SAB-PO Kit; Nichirei, Tokyo, Japan). The primary antibodies used were polyclonal antibodies to CysLT1 and polyclonal antibodies to CysLT2 (Acris Antibodies, Inc., San Diego, CA, USA).

Results

We first checked for the presence of mast cells in the tissue specimens prepared from 47 cases of human gynecologic malignant tumors (endometrial carcinoma (n = 16), cervical squamous cell carcinoma (n = 18), and ovarian high-grade serous carcinoma (n = 13)). In all tumor samples analyzed, numerous mast cells were diffusely distributed within the tumor. Such a diffuse distribution was very similar to that of mast cells in the lesions of other malignant and benign tumors that we previously studied (Figure 1). Immunohistochemical staining for CysLTs showed that CysLT-positive cells were diffusely distributed within the tumor tissue in all human malignant gynecologic tumors. Positive reactivity to the anti-CysLT antibodies was detected not only in tumor cells, but also in fibroblasts, mast cells, and endothelial cells (Figure 2). All these human malignant gynecologic tumors that we examined showed expression of these receptors like that of the other malignant and benign tumors that we previously studied. These findings were common to all tumors, and no marked differences were seen in non-tumor areas in the same specimens.

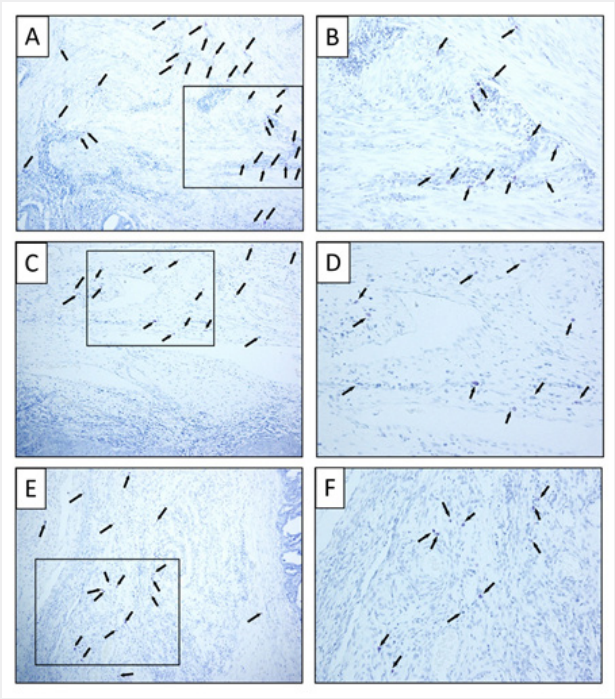

Figure 1: Detection of mast cells in human gynecologic malignant tumors (endometrial carcinoma, cervical squamous cell carcinoma and ovarian high-grade serous carcinoma) by toluidine blue staining. Positively stained cells (Violet color: arrows) are mast cells.
A. Endometrial carcinoma. (Mag: 100x)
B. Endometrial carcinoma. The microgram which escalated the square frame of figure A. (Mag: 200x)
C. Cervical squamous cell carcinoma. (Mag: 100x)
D. Cervical squamous cell carcinoma. The microgram which escalated the square frame of figure C. (Mag: 200x)
E. Ovarian high-grade serous carcinoma. (Mag: 100x)
F. Ovarian high-grade serous carcinoma. The microgram which escalated the square frame of figure E. (Mag: 200x).

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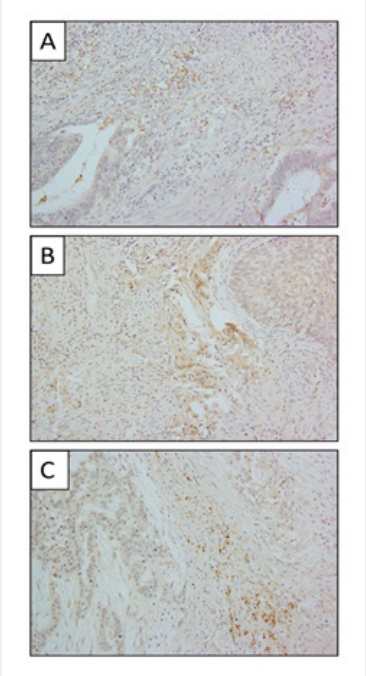

Figure 2: Detection of CysLT expression in human gynecologic malignant tumors (endometrial carcinoma, cervical squamous cell carcinoma and ovarian high-grade serous carcinoma) by immunohistochemical staining. The brown coloer denotes positive staining.
A. Endometrial carcinoma. (Mag: 200x)
B. Cervical squamous cell carcinoma. (Mag: 200x)
C. Ovarian high-grade serous carcinoma. (Mag: 200x)

Discussion

Mast cell infiltration and expression of leukotriene receptors were found in all tumor tissues that we examined at this time. These results are similar to pathologic findings (they were confirmed in various tumor tissues) that we previously reported. These results support the following discussion, which is like what we described in our previous report [1-3]. The leukotriene response that is caused by mast cell infiltration is an important mechanism of tumor progression in all tissues (Figure 3). Like other malignant tumors, infiltration of mast cells is found in the stromal area of the tumor tissue and is thought to induce stromal hyperplasia. This seems to lead to tumor progression. Leukotriene receptor-positive cells were diffusely found throughout the tumor tissue area, including stromal fibroblasts, vascular endothelial cells, and tumor cells in the parenchyma. Also, the leukotriene receptor positive cells were diffusely found in the whole tumor tissue including stromal fibroblasts and vascular endothelial cells as well as the tumor cells which were parenchyma.

But these cells are present in normal tissue and take the structure. If the leukotriene receptor expresses like a tumor tissue to these cells of the normal tissue, the receptor antagonist will show some inconvenient responses. However, in the same individual, the leukotriene receptor was confirmed only to a tumor tissue. And these results were found in not only the malignant tumor but also uterine myoma or endometriosis, and the like similarly [4]. In other words, this receptor is thought to express only in an area causing abnormal proliferation and is thought to be one of the factors inducing the abnormal proliferative lesion. Therefore, the leukotriene receptor antagonist will be effective for the treatment target of these proliferative lesions. We detected mast cell infiltration and leukotriene receptor expression in not only the uterine myoma but also endometriosis [1,4]. Based on these findings, we performed an animal experiment and clinical trial, and confirmed that a leukotriene receptor antagonist is effective for treatment of endometriosis [4-8]. We include endometriosis as a proliferative lesion, like a tumor pathologically, and we consider it to be a precancerous lesion. Therefore, the leukotriene receptor antagonist will have high effect of treatment for the gynecologic malignancy like effect of treatment for endometriosis.

The leukotriene receptor is a G protein-coupled receptor (GPCR), which has attracted attention recently as a drug discovery target. Some highly effective drugs have been developed that target GPCRs, including a leukotriene receptor antagonist that is effective for asthma. Thus, antagonists are more likely to be effective treatments if GPCRs are specifically present in the lesion. After confirming that leukotriene receptors are expressed in spontaneous breast cancer in rats, these rats were treated with antagonists, which had an antitumor effect [3]. The action target

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of the antagonist was thought to be only the tumor lesion area because the receptor was present only in the tumor lesion. Rats that developed breast cancer and that were given the antagonist showed no remarkable findings (no side effect of the drug) other than in the tumor tissue area [3]. The malignant gynecologic tumors (cervical cancer, uterine cancer, ovarian cancer) that we examined in this study have different carcinogens and characteristic mechanisms. For example, cervical cancer is related to virus infection, uterine cancer is related to estrogen, and ovarian cancer is related to genetic factors and pregnancy parity. However, pathologic findings common to all the tumor tissues, including mast cell infiltration and expression of the leukotriene receptor, were found. Thus, even in cancers that vary in terms of the process of carcinogenesis and tumor extension, the tumor can be inhibited by controlling the leukotriene receptor response (Figure 3).

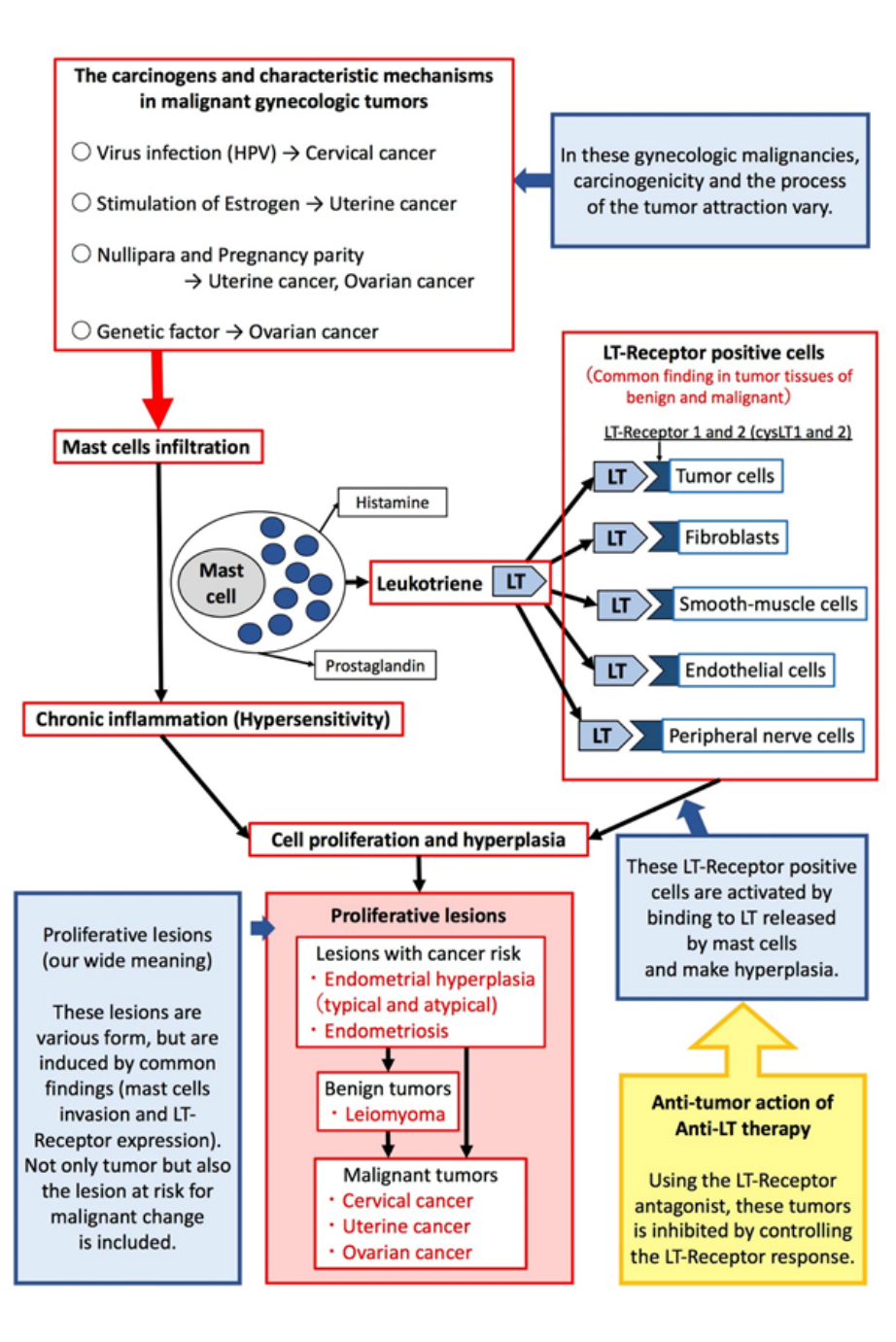

Figure 3: Mechanism of oncogenesis and extension in gynecologic tumors: the relation of mast cells and leukotriene receptor.

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In addition, the very interesting finding is that the leukotriene receptor is present in the lesion area in any stage multiplying pathologically: these are malignant tumors, benign tumors, precancerous lesions, and the like. It shows that we can use a leukotriene receptor antagonist for the patients of various stages. The patients of the terminal stage, which cannot anticipate the effect of the present therapy, may obtain effective treatment using the antagonist. And these receptors are confirmed to not only tumor cells but also the interstitial cells (a blood vessel or nerves, etc.) in tumor tissue constitution. So, this antagonist will make tumor size small in relatively short duration of treatment. Besides, there is no side effect. Therefore, it is thought that anti-leukotriene therapy is useful not only as a main therapy but also as neoadjuvant therapy [9,10].

Our findings confirm that the pathologic findings are common to almost all tumors (malignant and benign). After our reports about the relationship between various tumors and leukotriene receptors, an epidemiological analysis using a large Taiwanese healthcare database was reported. In this cohort study, the authors compared the cancer incidence in users and non-users of leukotriene receptor antagonists. This report showed that leukotriene receptor antagonist administration significantly decreased the risk of various malignant tumors [11]. Leukotriene receptor antagonists may become a novel type of oncotherapy in the future for the treatment of various tumors. Data from clinical trials is accumulating. In our unpublished study, we obtained good effects following treatment for some malignant tumors. We also applied for and received a patent for leukotriene therapy as an antitumor therapy globally. We believe that leukotriene therapy may become an excellent choice for oncotherapy.

Conclusion

In our study, these malignant gynecologic tumors have different carcinogens and characteristic mechanisms, however, the pathologic findings common to all the tumor tissues, including mast cell infiltration and expression of the leukotriene receptor, were found. There is a possibility that these tumors can be inhibited by controlling the leukotriene receptor response.

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