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Possibility of the Strategic Treatment for Various Tumors using the Leukotriene Receptor Antagonist: Discussion Based on the Common Pathologic Findings that Mast Cells and Leukotrienes are Involved in the Development and Proliferation of Tumors

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Abstract

The leukotriene receptor antagonist is indicated with a therapeutic drug of asthma and is one of the antiallergic agents. We found that mast cells and a leukotriene receptor commonly emerged for various malignant and benign tumors and proved that the allergic reaction was strongly associated with development and proliferation of tumors. And we experimented on the effect of treatment of the leukotriene receptor antagonist for spontaneous rat tumor and confirmed the efficacy. Our data show a wide effect of this medicine and the fewer side effects and will cause a discussion for the chemotherapy of the current malignant tumor. This commentary briefly summarizes about current evidence and future prospect in the oncotherapy of the leukotriene receptor antagonist.

Keywords: Mast cell; Allergy; Leukotriene; Apoptosis; Tumor; Oncotherapy

Background and Introduction

Surgery, chemotherapy, and radiotherapy are the standard regimen for malignant tumors, but the number of people who die of a malignant tumor continues to increase, and new and prophylactic therapies are needed.

Several factors associated with various inflammatory processes are involved in the proliferation mechanisms of tumors. Cyclooxygenase is one of the factors associated with inflammation that has attracted attention, and an attempt to use anti-inflammatory analgesics including aspirin, which inhibits cyclooxygenase, to treat malignant tumors has been performed. The risk of colorectal cancer decreased markedly in humans who used aspirin regularly, and an improvement in benign adenoma has been observed in laboratory animals after aspirin administration [1-3].

Prostaglandin is involved in allergic inflammatory reactions, and we found that allergic inflammation with mast cell invasion is associated with oncogenesis and the proliferation of malignant tumors in particular [4]. Medications that inhibit prostaglandin, which is produced by cyclooxygenase, may also be useful for treating malignant tumors. The medication as the anticancer drug of the anti-inflammatory analgesic is a long term, there are fewer side effects of the anti-inflammatory analgesics than that of anticancer drug, but there is it. Consequently, the clinical application of anti-inflammatory analgesics for the treatment of malignant tumors and as preventive medicine is restricted.

Histamine is another mast cell-related factor. Histamine is present in tumor cells, and antihistamines reinforce the effect of anticancer drugs [5]. However, the antitumor effects of antihistamines have not been thoroughly described.

In addition to cyclooxygenase, another factor associated with inflammation is leukotriene, which together with its receptor, are an important focus of asthma bronchial treatment. The effects of the leukotriene receptor and leukotriene receptor antagonists on tumors have been examined [4,6].

We discovered invasion of mast cells into tissues with endometriotic lesions [7] and elucidated the effect of treatment with a leukotriene receptor antagonist [8,9]. Endometriosis is a benign condition. We determined the commonality between endometriosis and tumor cells, which are both proliferative lesions.

Examination and Discussion

We conducted the following examination [4,6].

1. Examination using the spontaneous breast cancer rat

After staining naturally occurring breast cancer tissue from a Sprague-Dawley rat and confirming the breast cancer microscopically, we observed invasion of mast cells and expression of leukotriene receptors (cysteinyl leukotriene receptor (CysLT)1 and 2) in the tumor and interstitial cells. Furthermore, various leukotriene receptor antagonists including Zafirlukast (1.33 mg/kg/day), Monterukast sodium (0.16 mg/kg/day), Pranlukast hydrate (7.5 mg/kg/day), and Zileuton (34.3 mg/kg/day) induced apoptosis in tumor and interstitial cells when given to these rats for 3-7 days. These drugs also inhibited angiogenesis and neuropoiesis in the tumor tissue. These effects were not found in normal tissue.

2. Examination using various human tumor tissues (malignant and benign)

We stained four types of benign tumors and 22 types of malignant tumors and examined them microscopically. In all tissues, we observed

invasion of mast cells and leukotriene receptor (CysLT 1 and 2) expression.

3. Examination of the relationship between the grade and leukotriene receptor expression in human colon polyps (benign adenoma)

After staining polyps from 30 colon cases (histopathology classification: Low grade, 15 cases, High grade, 15 cases) and assessment of the histology by pathologists, we observed invasion of mast cells and leukotriene receptor expression in all polyps. We also observed that the degree of mast cell invasion and the expression of leukotriene receptors were correlated with the histological classification.

These results showed that mast cell invasion and leukotrienes receptors were strongly associated with development of tumor tissue and malignant transformation of benign tumors (Figure 1). In other words, the factors that induce the development of tumors vary, but the phenomena that cause them are common (mast cell invasion and leukotriene response). These factors are thought to be connected to growth and malignant transformation of tumor tissue. We hypothesized that leukotriene receptor antagonists would treat tumor tissue and prevent malignant transformation *via* these common phenomena. Our experiment showed that leukotriene receptor antagonists were effective for treating tumor tissue in laboratory animals.

Our experiment also showed that the antitumor effects involved apoptotic death and inhibition of angiogenesis and neuropoiesis. Angiogenesis inhibitors are associated with severe side effects and are not yet established as anti-tumor agents. Our findings have not been confirmed in tumor tissue other than tissue in the animals we treated. However, our early experiments suggest that leukotriene receptor blockers may become anticancer drugs with very few side effects. Also, in oncotherapy, the concept of inhibiting neuropoiesis is novel and may also provide pain relief for terminal patients.

Regarding prevention of malignant transformation in patients at elevated risk for malignant transformation, the data from colon polyps, which are benign adenomas, are very interesting. The association between histopathological classification and risk for malignant transformation is well-known, but we may more precisely understand the risk for malignant transformation in patients after assessment of mast cell invasion, leukotriene receptor expression, and histopathological classification. Leukotriene receptor antagonists may be effective as preventive medicine for malignant transformation. Epidemiological findings have shown that malignant tumor risk decreases in asthmatic patients who regularly take leukotriene receptor antagonists [10]. Indeed, the incidence of some cancers in these patients decreased markedly, with the rate of decline depending on the remedy dose. Consequently, this medicine is expected to be made available as a preventive medicine for malignant tumors.

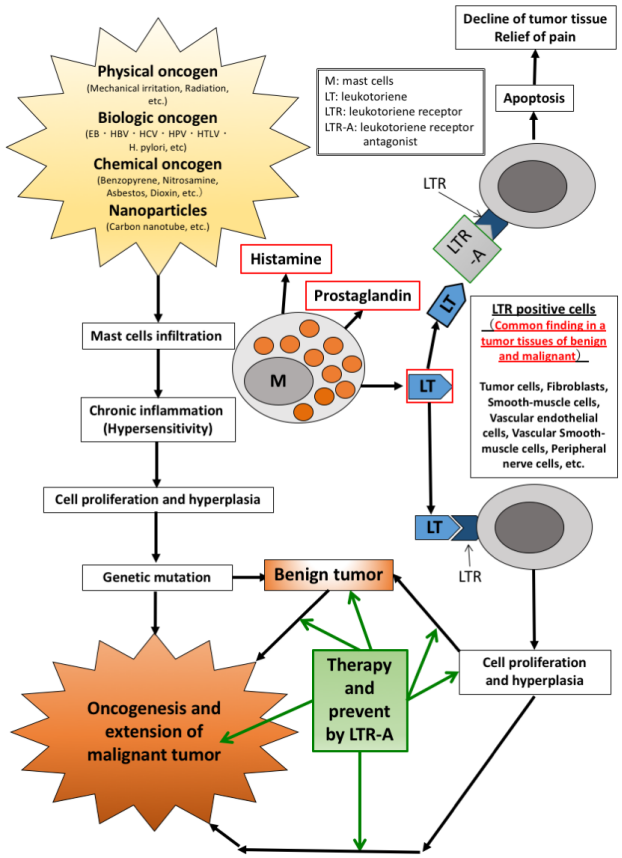

Figure 1: Illustration of the mechanism that is led by our study in oncogenesis of tumors: the relation of mast cells and leukotriene receptor.

Future Prospects

Leukotriene receptor antagonists are widely used to treat asthma and allergic rhinitis, and their safety has been established. Leukotriene receptor antagonists may become useful for treating various tumors, as suggested by our experimental observations. Leukotrienes are associated with angiogenesis in inflammatory conditions such as asthma [11,12], and therefore, our observations of inhibition of angiogenesis and neuropoiesis with this antagonist are very interesting.

Although this is a closed trial, we have already administered the leukotriene receptor antagonist to several terminal patients, who were diagnosed as being unlikely to show any improvement, with pancreatic cancer and gastric cancer, even if conventional treatment was offered. These patients have all showed remarkable results in terms of treatment and we are currently preparing a clinical trial. As a future therapy for tumors, combination therapy with leukotriene receptor antagonists alone or other drugs is expected. We also hope that preventive medicine will be developed that prevents malignant transformation of benign tumors.

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