TGF-β1 in breast cancer-estrogen regulation

KEYWORDS: Breast Neoplasms; Transforming Growth Factor beta; Estradiol

ABSTRACT

TGF-β1 is a pluripotent cytokine with diverse effects in the normal development of mammary glands, and in the development of malignant tumors of the breast. The aim of the study was to determine the levels of TGF-β1 in the group of advanced breast cancer, in which increased TGF-β1 levels were most likely to be expected. TGF-β1 levels were also compared with estradiol levels. Our results suggested that TGF-β1 synthesis may be regulated by estrogen or anti-estrogen through ER. Finding of increased TGF-β1 levels, due to its possible role in predicting invasive phenotype in later phases of tumor progression, may indicate the tendency of tumor tissue towards automy.

INTRODUCTION

TGF-β1 acts as a tumor suppressor in the initial phase of tumor development, while in the later phases it starts to act as a tumor promoter. In our study, we intended to determine if there is a statistically significant increase of TGF-β1 plasma levels in the group of advanced/metastatic breast cancer patients, as this is the group in which such an increase would be most likely to be expected. The second part of this report deals with the possibility that the increased plasma concentration of TGF-β1 may be in correlation with estradiol levels.

TGF-β1 is a pluripotent (multifunctional) cytokine with such a diverse or opposing effects that its role in vivo is difficult to understand under normal physiological conditions as well as in pathophysiological processes and cancer states. Its effect is pleiotropic, concentration dependent, cell environment dependent and may be indirect. It is of special significance since it represents the most potent physiological inhibitor of cell proliferation (epithelial cells). On the other hand, it may also act as a mitogen stimulus for the proliferation of fibroblasts; it can induce apoptosis of various types of cells, or it affects tissue morphogenesis regulating the deposition of extracellular matrix and tissue remodeling (1). TGF-β1 acts via specific TRI and TRII receptors, serine-threonine kinase, from which the signal is conducted through a very complex network of intracellular mediators (Smad). Through a direct effect on DNA, interaction with DNA-bound proteins and with various cofactors and corepressors, they enable such a wide spectrum of cell response (2).

It has been confirmed that TGF-β1 is involved in the normal development of mammary glands (breasts) and thus it is logical that it has an effect in the development of malignant tumors of the breast. The basic hypothesis on the role of TGF-β1 in the progressive breast tumor is related to the dual nature of this molecule. In the initial phases of tumor development, while the malignant cells are still capable of reacting to its inhibitory effect, TGF-β1 acts as a tumor suppressor. In the later phases, due to inactivation mutations of their receptors or intracellular mediators, malignant cell become resistant to its inhibitory effect. Because of that TGF-β1 starts to act as a tumor promoter in an autocrine (clonal selection of malignant cells) and in a paracrine (enables tumor invasion, through the effect of angiogenesis, tissue reconstruction and immune system) manner (3).

In our study, we intended to determine if there is a statistically significant increase of TGF-β1 plasma levels in the group of advanced and metastatic breast cancer patients, as this is the group in which such an increase would be most likely to be expected. The second part of this report deals with the possibility that the increased plasma concentration of TGF-β1 may be in correlation with estradiol levels.

MATERIALS AND METHODS

TGF-β1 levels were measured by the Quantikine ELISA kit in platelet-poor plasma samples of 44 advanced and metastatic breast cancer patients, performed according to the manufacturer's protocol. Concentrations of 17-β estradiol were determined by using ELISA-microwell method (DIALAB), and estrogen receptor content was determined by using biochemical (DCC) method.

The Spearman rank correlation test and Mann-Whitney U test were used to assess the existence of significant statistical differences between the patient subgroups (according to clinical and pathological parameters) and the possible correlation between the levels of TGF-β1 and estradiol.

RESULTS AND DISCUSSION

The question of increased TGF-β1 plasma levels in the case of breast cancer is still open, since there are still controversial results in the literature. Also, most data deal with the induction of TGF-β1, as a response to antiestrogen stimulation, while there are less data on the possible estrogen dependence on TGF-β1 synthesis. Our results (4) (in press) confirmed the existence of statistically significant differences between the analyzed group of patients and control group. In the patient groups, the group of postmenopausal patients contributes most to the statistical difference. In this specific group, we analyzed and detected the existence of a significant correlation between the plasma levels of estradiol and TGF-β1 in ER positive patients (Figure 1).

Since TGF-β1 is definitely involved in the etiology of breast cancer, which belongs to hormone dependent tumors, it is logical that our presumption is that its production may be regulated by estrogen (but also antiestrogen) (5). It has been shown that in normal breast tissue, it is TGF-β1 that regulates the normal growth of lactating epithelial tissue, acting as a regulating factor of ER positive cell proliferation (which in normal tissue presents only a small percentage of cells) under conditions of hormone regulation (1). The activation of TGF-β1 may be regulated by steroid hormones and this happens in ER positive cells, although these cells do not proliferate. Almost all of ER positive cells are also TGF-β1 positive, during hormone stimulation. The analysis of the TGF-β promoter sequence showed the existence of ERE (estrogen response element) in the 5' upstream region of the TGF-β gene (6). ERE sequences represent binding sites for ER which acts as a hormone-activated transcriptional regulator by which both the estrogens and antiestrogens exert their effect. It is most probable that the transcriptional mechanism-estrogen-ER complex reacts differently from the antiestrogen-ER complex, through the interaction with factors which are specific for one or the other complex. The level of hormonal control of TGF-β1 may be not only transcriptional, but there may be
also a posttranscriptional control or even a control of activation of the TGF-β1 latent form into the biologically active form.

As TGF-β1 synthesis may be regulated by estrogen or antiestrogen through ER and because in postmenopausal women (independent on the concentation of plasma estradiol) there are mechanisms which enable the maintenance of higher levels of estradiol concentrations in tumor tissue (7) (as an adaptation of the tumor cell enabling a higher degree of proliferation) then it is logical to assume that this increased estradiol concentration induces an increased TGF-β1 synthesis. However, as it is known that TGF-β1, due to its multifunction, in later phases of tumor progression, behaves as an invasive marker, this may potentiate the tendency of tumor tissue towards autonomy.

Acknowledgement:
This work was supported by grant provided by the Ministry of Sciences, Technology and Development of Serbia, "Molecular biomarkers of estrogen (in)dependent breast cancer: biological and clinical aspects", No 1598.

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The importance of simultaneous determination of breast cancer biomarkers

KEYWORDS: Breast Neoplasms; Tumor Markers, Biological

ABSTRACT

It is shown that steroid hormone receptors by themselves are not sufficiently strong prognostic factors in management of breast cancer. For that reason, simultaneous consideration of different biomarkers seems to be more appropriate for clinical use, i.e. selections of patients with high/intermediate/low risk of disease outcome. However, the amount of tumor material available from breast carcinoma can preclude determination of estrogen-regulated biomarkers together with estrogen receptor and progesterone receptor. The aim of this study was to assess the possibility of estrogen receptor and progesterone receptor determination by a single-point instead of five-point biochemical method. Our results demonstrated that the correlation between measurements of estrogen and progesterone receptor contents obtained by the five-point and single-point assay in the total population was very high. Consequently, we could use the single-point assay instead of five-point assay for estrogen receptor and progesterone receptor determination, thus making possible determination of other molecular biomarkers from the same breast carcinoma.

BREAST CANCEROGENESIS

Over 85% of the spontaneous mammary cancers that occur in women originate in the luminal mammary epithelial cells (LMECs). Mammary cancers are classified (1,2) according to their requirement for proliferation as being either hormone-dependent tumors or hormone-independent tumors. Whether a cancer is a hormone-dependent tumor or a hormone independent tumor is ultimately based on the response to hormone therapy of metastatic disease. Hormone dependent tumors require the presence of hormones for their proliferation, whereas hormone independent tumors do not. Why are hormones required and how do they regulate the genesis of mammary cancers of heterogeneous phenotypes, including hormone dependent tumors and hormone independent tumors?

It is well established that hormones from several endocrine glands act as key regulators for LMEC proliferation (3,4). Besides hormones, it seems that

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The manuscript was received: 01.10.2002.
Accepted for publication: 10.10.2002.