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# A Review on the less Investigated Protumoral Molecules of the Human Body

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## Abstract

In addition to the well protumoral role of estrogens, androgens and tumor growth and angiogenic factors, other potential endogenous protumoral molecules would have to be taken into consideration in the therapy of cancer, namely PRL, GH, beta-endorphin, ADH, PTHrP, ET-1 and TGF-beta. Because of its concomitant effects on cancer cell proliferation, angiogenesis and anticancer immunity in an immunosuppressive way, the control of TGF-beta secretion and activity could constitute a central and a key-point in the treatment of human neoplasms.

## Keywords

Endothelin-1; Immunosuppression; Parathyroid hormone-related protein; Transforming growth factor-beta

## Introduction

With the advances in the knowledge of the cellular and immune mechanisms responsible for tumor onset and progression, it has appeared that the main molecules provided by anti-cancer or protumoral activity may be identified within the human body, which contains several factors with inhibitory or stimulatory action on cancer cell proliferation and differentiation, as well as with stimulatory or suppresssive effects on the anticancer immunity. Therefore, from an imaginary point of view, the enigma of the resolution of cancer would have to be primarily identified within the same human body. At present, according to the knowledgements available up to now, the anticancer immunity is mainly mediated by TH1 (CD4+) lymphocytes through the release of IL-2, cytotoxic T lymphocytes (CD8+), NK-LAK cells [1], and mature dendritic cells by acting as antigen presenting cells and producing IL-12 [2], whereas it has suppressed by the regulatory T lymphocytes (T reg) (CD4+CD25+) (T reg) [3] through the secretion of immunosuppressive molecules, such as TGF-beta, IL-10 and IL-35, and the monocyte-macrophage system by producting several inflammatory immunosuppressive molecules, namely IL-6, IL-1 beta and TNF-alpha [4]. Most cytokines may act as potential antitumor or protumoral endogenous factors. Therefore, by considering their dual effects of the anticancer immunity and on the inflammatory response, the most known cytokines may be subdivided into three major subgroups: 1) immunosuppressive anti-inflammatory cytokines: TGF-beta and IL-10; 2) immunosuppressive inflammatory cytokines: IL-6, IL-1 beta, TNF-alpha; 3) immunostimulatory inflammatory cytokines: IL-2 and IL-12, which may respectively activate the NK-LAK system- mediated antigen independent antitumor cytotoxicity, and the antigen-dependent cytotoxicity exerted by cytotoxic T lymphocytes. In any case, it has to be taken into consideration that IL-2 and IL-12 may also play anti-inflammatory effects, because of the possible stimulatory action of IL-2 on TGF-beta release from T reg cells, and the inhibitory effect of IL-12 on IL-17 secretion from TH17 lymphocytes [5]. Obviously, in addition to the protumoral cytokines, the most active protumoral molecules of human body are mainly represented by the same tumor growth factors, namely EGF, PDGF and FGF, and the sexual hormones, such as the estrogens for breast cancer and the androgens for prostate cancer, as well as the angiogenic factors, in particular VEGF, which may exert both angiogenic activity and immunosuppressive effect by inhibiting dendritic cell differentiation [6]. Metabolic factors, such as the biliary acids, may promote tumor development. Moreover, it has to be remarked that in addition to the well known protumoral activity of estrogens and androgens, several other endocrine-like substances are provided by potential protumoral mechanisms, whose importance, however, has not been taken into consideration up to now by the clinical Oncology in the management of cancer cure. These molecules are namely represented by PRL for breast and prostate cancers [7], FSH for ovarian cancer [8], parathyroid hormone-related protein (PTHrP) [9] and at least in part parathyroid hormone (PTH) itself [10], vasopressin (antidiuretic

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hormone: ADH) [11], endogenous mu-opioid agonists, such as beta-endorphin [12], and endothelin-1 (ET-1) [13]. Finally, some other endogenous molecules, namely vitamin D3, may have a dual action on cancer growth, due to its possible inhibitory action on cancer cell proliferation and its immunosuppressive activity on the anticancer activity, which is mediated by the stimulation of T reg cell system, with a following enhanced TGF-beta secretion [14].

## Protumoral activity of parathyroid hormone-related protein and parathyroid hormone

PTHrP is produced by several cells in response to the stimulatory action of PTH [9]. Most of the metabolic and proliferative effects of PTH are namely due to the action of PTHrP produced in response to PTH itself [9], including hypercalcemia and stimulation of cell proliferation. PTHrP may play a protumoral activity by either exerting a direct stimulatory effect on tumor cell proliferation in PTHrP receptor expressing tumors [9,15,16], or by suppressing the antitumor immunity trough the stimulation the release of immunosuppressive cytokines, such as IL-6 [15] and TGF-beta [17]. PTHrP has also appeared to be involved in the mechanisms responsible for the onset of the neoplastic cachexia [15]. Finally, PTRrP may promote the angiogenesis by interacting with VEGF itself [17]. Therefore, cytokines, endocrine-like substances and cell growth factors may stimulate tumor growth by acting at least in part through a modulation of PTHRrP secretion and activity. The secretion of PTHrP may be inhibited by vitamin D3 [9], and this effect may explain at least in part the antiproliferative action of vitamin D3 [14]. PTHrP secretion would be stimulated by estradiol and progesterone, and inhibited by corticosteroids because of their stimulatory and inhibitory effects, respectively, on PTH release [18]. Then, by considering its stimulatory effects of tumor cell proliferation and angiogenesis, and its inhibitory action of the anticancer immunity, it is not surprising that the evidence of abnormally blood levels of PTHrP or tumor expression of PTHrP receptors have appeared to be associated with a poor prognosis and a reduced survival in advanced cancer patients [19-21], including the most aggressive human neoplasms, such as brain tumors and triple negative breast cancer (TNBC). The protumoral action of PTHrP is also confirmed by the evidence that the concomitant administration of anti-PTHrP monoclonal antibody may enhance the cytotoxic activity of cancer chemotherapy [21]. As far as the action of PTH, irrespectively of its interactions with PTHrP, it has appeared that immune cells may express PTH receptors and that PTH may also play a minimal protumoral activity by inhibiting T cell proliferation and functions [10].

## Protumoral effects of vasopressin and endothelin-1

In addition to its fundamental role in inducing fluid retemption, a stimulation of hypothalamus-pituitary-adrenal axis, and an enhancing effect on blood pressure, ADH would play a preferential stimulatory effect on tumor progession by influencing the immune functions through a stimulation of ET-1 release [13], which may suppress the anticancer immunity. Moreover, ADH would promote cancer progression by stimulating the angiogenic processes [22]. ET-1 would constitute one of the main endogenous protumoral molecules [13], since it may stimulate tumor growth through all possible protumoral mechanisms identified up to now, consisting of direct stimulation off cancer cell proliferation by acting as a tumor growth factor or a stimulating factor for other tumor growth factor, angiogenic activity by stimulating VEGF secretion and activity [23], and immunosuppressive inflammatory action due to the stimulation of inflammatory cytokine secretion, namely IL-6 [13,24]. Then, the well known promoting effect of stress on tumor onset and growth would be mainly due to ET-1 itself [25], because of its fundamental role in activating the sympathetic system in stress conditions [13].

## Prolactin and tumor growth

It is known that PRL may act as tumor growth factor at least for breast and prostate carcinomas by interacting with IGF-1 activity [7]. However, despite this evidence, at present no clear antitumor strategy carried out to control PRL release has been standardized in the treatment of cancer patients, namely because of the unclear role of PRL-receptor (PRL-R) expression by tumor cells. In fact, either a negative or a positive prognostic significance of PRL-R expression have been reported in breast cancer patients [26]. At present, it has been shown that the evidence of abnormally high PRL blood concentrations have appeared to predict lower survival and response to therapy in metastatic breast cancer patients [27], including those with TNBC [28]. On the contrary, the evidence of no post operative hyperprolactinemia may predict a worse prognosis, because of the absence of PRL increase in response to breast manipulation such as breast surgery would reflect the existence of an already altered neuroendocrine control of mammary tumor growth [29]. On the contrary, the role of GH in human tumors is still controversial and complex, because its role in the control of main tumor growth factor secretion, such as EGF, is still unclear, and at present the antitumor therapeutic approach carried out to act on GH-IGF-1 system is limited to the use of somatostatin analogues in the treatment of somatostatin receptor expressing neuroendocine tumors.

## FSH and gynecologic tumors

The enhanced frequency of ovarian cancer and endometrial adenocarcinoma in post menopausal women could be due at least in part to menopausal status- associated enhanced secretion of FSH, which could stimulate ovarian epithelial cell proliferation [8], and FSH levels could negatively correlate with the prognosis of gynecologic tumors, even though there are controversial results in the literature. FSH levels have appeared to play a negative prognostic significance also in patients with breast cancer [30], because of its correlation with HER 2-expression, while no correlation has been seen with PRL-R expression. LH would have less proliferative effects with respect to FSH [31]. On the contrary, the anti-mullerian hormone (AMH) would exert an anticancer activity, and AMH high levels have appeared to be associated with a more favourable prognosis in ovarian cancer [32].

## The potential tumoral activity of beta-endorphin

The chronic stimulation by mu-opioid agonists, including beta-endorphin itself, have been proven to directly stimulate cancer cell proliferation and tumor neo angiogenesis [12], as well as to inhibit the anticancer immunity by stimulating T reg cell system, with a following increase in IL-10 and decline in IL-2 and IL-12 concentrations [33]. The protumoral role of mu-opioid agonists is confirmed by the evidence that the protumoral influence of stress may be abrogated by the concomitant administration of mu-opioid antagonists, such as naloxone and naltrexone [34]. Finally, the expression of mu-opioid receptor by brain tumors has been shown to predict a more severe prognosis [35].

## The fundamental protumoral role of TGF-beta

At least from a theoretical point of view, TGF-beta would represent the main endogenous protumoral molecular of human body [3]. This statement is justified by the fact that TGF-beta, as well as ET-1, may stimulate cancer progression through the overall main known biological protumoral mechanisms, including a stimulation of cell proliferation and angiogenesis, and inhibition of the anticancer immunity by blocking TH1, dendritic cell and cytotoxic T lymphocyte functions [36]. TGF-beta may stimulate the neoangiogenic processes by influencing the intercellular matrix composition [37]. TGF-beta has also appeared to exert an antiproliferative activity, but this effect would be limited to the early phases of cancer development [3,36]. In particular, TGF-beta could counteract cytotoxic and TH1 lymphocyte infiltration into tumor mass, by opposing tumor cell destruction [38].

## Conclusions

The evidence of several endogenous protumoral molecules would have to modify the clinical approach to cancer therapy, carried out to control their secretion and activity, whereas at present the only endocrine-like approach to cancer cure would regard the only estrogens, androgens and tumor growth factor, namely EGF.

Moreover, it has to be remarked that some of tumor promoting effects of other protumoral molecules, namely PTHrP itself, could be mediated at least in part by TGF-beta. Therefore, the control of TGF-beta activity by TGF-beta antagonists, TGF-beta receptor antagonists and anti-TGF-beta monoclonal antibodies, could constitute a key point to control cancer progression. Similar considerations may be proposed for ET-1, because of its influence on both cell proliferation and angiogenesis and the evidence of interactions between TGF-beta and ET-1 secretions and activities.

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