Elevated Plasma Platelet-derived Growth Factor B-Chain Levels in Cancer Patients

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ABSTRACT

Platelet-derived growth factor (PDGF) is produced by a variety of normal and tumor cells in vitro. We have developed an enzyme-linked immunosorbent assay for the detection of the B-chain of PDGF. This assay can reliably detect 0.1 ng/ml of homodimeric recombinant PDGF B-chain and does not cross-react with recombinant PDGF-AA, epidermal growth factor, basic fibroblast growth factor, or transforming growth factor-β. Citrated plasma from 72 control individuals had a PDGF B-chain (PDGF-B) level of 0.32 ± 0.14 ng/ml (mean ± SD) with a range of 0.10–0.69 ng/ml. The plasma platelet factor 4 (PF4) level was 97 ± 30 ng/ml, with a range of 34–363 ng/ml. Citrated plasma was obtained from 131 cancer patients, and plasma PDGF-B was elevated in 19 (15%) of the patients. Both PDGF-B and PF4 were elevated in 14 (11%) of these patients, consistent with a platelet source of PDGF-B. In 5 patients (4%), however, PDGF-B was elevated and PF4 was not elevated compared to the control group. This last group of patients may have a tumor-derived source of PDGF-B which could be important in autocrine or paracrine growth stimulation of the tumor cells.

INTRODUCTION

PDGF was first described as a factor of platelet origin that stimulated the growth of fibroblasts (1) and smooth muscle cells (2) in cell culture. Subsequently, a growth factor from platelets was reported to stimulate the growth of normal human glial cells in culture (3). Further study has shown that PDGF is stored in the α-granules of platelets, is secreted during blood clotting, and is the major mitogen in serum for the growth of cells of mesenchymal origin. In addition to platelets, PDGF has recently been found to be secreted by other normal cells in culture, including activated macrophages, endothelial cells, and smooth muscle cells. PDGF has been implicated to play a role in wound healing, fetal development, cancer, atherosclerosis, and fibrosis (4).

Human platelet PDGF is an M, 30,000 dimeric glycoprotein composed of both A- and B-chains of approximately equal size. The genes for the A- and B-chains have been localized to chromosomes 7 and 22, respectively, and encode protein products with 60% amino acid sequence similarity (5, 6). Human platelet PDGF is composed predominantly of A- and B-chain heterodimers, with small amounts of PDGF-BB and PDGF-AA homodimers also present (7). All three isoforms of PDGF have full mitogenic activity, depending on the total and proportionate number of the two different PDGF receptor subunits, α and β, that are present on the target cells (8).

Interest in the relationship between growth factors and cancer intensified when it was discovered that the B-chain of PDGF and the predicted sequence of p28 Nis, the protein product of the sis oncogene of simian sarcoma virus, were virtually identical in amino acid sequence homology (9, 10). This discovery marked the first time that an oncogene was identified as a cellular gene of known function and lent further support to the autocrine theory of tumor cell proliferation.

The cellular site of the transforming action of v-sis remains controversial. Some reports have provided evidence in support of the hypothesis that the newly synthesized v-sis oncogene product binds to and activates the PDGF receptor in the intracellular compartment of the infected cell, while other studies have concluded that secretion of PDGF-like growth factors from the simian sarcoma virus-infected cell (or cell surface localization of internally activated PDGF receptors) is critical for mitogenic signaling (11). Regardless of the site of action, recent evidence shows that overexpression of the normal human PDGF B-chain gene (c-sis protooncogene) causes the generation of fibrosarcomas in mice (12), thus confirming the full oncogenic potential of an overexpressed normal PDGF-B gene in vivo.

Many human tumor cell lines of mesenchymal origin, such as sarcoma and glioblastoma cell lines (13), and human mesothelioma cell lines (14), have been reported to secrete PDGF-like proteins into the culture medium and therefore may be growth-stimulated in an autocrine fashion. PDGF-like molecules have also been found to be secreted by normal cell lines that have been transformed by a wide spectrum of agents, including viral, carcinogenic, and “spontaneous” events (15). Human breast cancer cell lines (16–18), prostate carcinoma cell lines (19), and melanoma cell lines (20) also synthesize and secrete PDGF-like proteins. Unlike mesenchymal cells, however, these cells do not possess PDGF receptors and do not respond mitogenically to PDGF. In this report, we present evidence that the PDGF B-chain concentration is elevated in the plasma of certain cancer patients.

MATERIALS AND METHODS

Subjects. One hundred thirty-one cancer patients (74 women and 57 men, ranging from 25 to 86 years of age) were included in this study. Only patients who recently diagnosed but untreated cancer or patients who received previous treatment but had progression of disease at the time of blood collection were selected. Informed consent was obtained from all subjects before venipuncture. All other medical problems and medications were recorded. The control group consisted of 72 healthy individuals, 44 women and 28 men, ranging from 19 to 76 years of age, with no history of cancer.

Plasma and Serum Preparation. Blood was drawn from the forearm by venipuncture with a 21-gauge butterfly needle connected to a mul...
tiple sample Luer adapter and tube holder (Baxter Scientific Products, McGaw Park, IL). Serum was collected first in a Vacutainer tube with no anticoagulant; plasma was then collected in 4.5-mL Vacutainer tubes that had 0.5 mL of a 3.8% solution of sodium citrate/tube as anticoagulant (Terumo Medical Corp., Elkton, MD). Patient and control blood samples were drawn by the same nurses using identical procedures. Automated platelet counts that were available from patient blood specimens collected within 24 h of the blood drawn for PDGF determination were recorded.

After venipuncture, the citrated anticoagulated blood was mixed and kept at 4°C for up to 3 h before being centrifuged. Preliminary experiments had shown that PDGF-B levels were not increased in control blood samples that were maintained in sodium citrate at 4°C for up to 7 h before centrifugation, whereas a 24-h blood incubation period yielded substantially increased PDGF-B levels in platelet-poor plasma, presumably due to platelet a-granule release (data not shown). The blood drawn for serum collection was kept at room temperature for at least 1 h (to ensure complete clotting) before centrifugation.

For platelet-poor plasma preparation, citrated blood was centrifuged at 500 x g for 10 min in a Beckman TJ-6 centrifuge that was precooled to 4°C. The supernatant (platelet-rich plasma) was collected with plastic transfer pipets and placed in polycarbonate Sorvall centrifuge tubes and centrifuged at 4°C at 4400 x g for 10 min in a precooled Sorvall RC-5 superspeed centrifuge. This supernatant (platelet-poor plasma) was carefully collected with plastic transfer pipets and then aliquoted into Falcon polystyrene tubes and stored at −70°C. This centrifugation protocol was sufficient to remove all platelets from the platelet-poor plasma, as determined by the virtually identical low PDGF-B levels obtained from control plasma that was assayed without freezing, compared with the same plasma after several freeze-thaw cycles (data not shown).

For serum preparation, the clotted blood tubes were centrifuged at 500 x g for 10 min, and the supernatant serum was collected, aliquoted, and stored at −70°C.

PDGF ELISA. PDGF B-chain levels in human samples were determined in a double antibody sandwich enzyme-linked immunosorbent assay (ELISA). Human recombinant B-chain PDGF (AMGen, Inc., Thousand Oaks, CA) was produced by transfection of Chinese hamster ovary cells with human c-sis protooncogene was used as a standard in the ELISA. This homodimeric human rPDGF-BB is homogenous and has been shown to be as active as human platelet PDGF on a molar basis using in vitro mitogenic and chemotactic assays (21). The antibody used in this ELISA was produced by immunization of a rabbit with v-sis homodimeric recombinant PDGF that was also produced in Chinese hamster ovary cells. The rabbit antisera was further purified on protein A-Sepharose and the IgG fraction was stored at 4°C until use. Part of the protein A-purified IgG fraction was biotinylated using biotin-1-aminocaproyl-N-hydroxysuccinimide ester (Pierce Chemical Co., Rockford, IL) at an approximate molar ratio of 10:1 (biotin:protein) (22). The epidermal growth factor, basic fibroblast growth factor, and transforming growth factor-β used for cross-reactivity studies were all obtained from Collaborative Research (Bedford, MA). Recombinant human A-chain PDGF was from AMGen, Inc.

The initial step in the ELISA was the addition of 100 μl of protein A-purified anti-v-sis rPDGF antibody (diluted to 20 μg/ml with 0.05 M sodium carbonate buffer, pH 9.6) to each well of flexible polyvinyl chloride 96-well microtiter plates (Dynatech Laboratories, Chantilly, VA). After overnight incubation of the plates at 4°C, the antibody solution was removed and the plates were washed four times with washing buffer (0.05% Tween 20 in PBS at pH 7.3). The plates were then blocked with 1.0% gelatin (Difco Laboratories, Detroit, MI) in PBS for 1 h at room temperature and then washed twice with washing buffer. Triplicate samples of rPDGF-BB standards (100 μl; diluted in 0.1% gelatin-PBS), citrated platelet-poor plasma (100 μl; undiluted), or human serum (100 μl; diluted 1:10 in PBS) were added to the wells and the plates were incubated overnight at 4°C. In some assays, rabbit IgG (50 μg/ml) was coincubated with the standards or plasma and serum samples to reduce nonspecific binding. After the wells were washed four times, they were incubated with 100 μl of a solution of a biotinylated preparation of the protein A-purified anti-v-sis that was diluted with 1.0% gelatin-PBS to a final concentration of 1 μg/ml. After incubation at room temperature for 1–2 h with gentle shaking, the plates were washed five times and 100 μl of avidin-horseradish peroxidase conjugate (Vector Laboratories, Inc., Burlingame, CA) that was diluted 1:500 in 1.0% gelatin-PBS was added to each well. After a 30-min incubation with gentle shaking, the plates were washed six times and the wells were incubated with 100 μl of substrate solution for 4.5 min at room temperature. The substrate solution was composed of o-phenylenediamine, 1 tablet in 10 ml diluent solution (Abbott Laborato ries, Inc., North Chicago, IL). Substrate conversion was arrested by the addition of 50 μl of 1 N HCl, and substrate absorbance was determined at a test wavelength of 490 nm and a reference wavelength of 630 nm using an EL 312 microplate reader (Bio-Tek Instruments, Inc., Winooski, VT).

Linear regression analysis was conducted on the standard curves from each plate, and the calculated correlation coefficients equaled or exceeded 0.98 in all assays. The PDGF-B concentration in plasma and serum samples was then calculated from the linear regression data. The interassay variability for the PDGF-B ELISA was calculated using the PDGF-B values obtained by assaying an identical serum aliquot (diluted 1:20 in PBS) from the same control individual in each of 9 ELISAs. The mean ± SD of the PDGF-B value was 13.55 ± 2.12; the coefficient of variation was 15.7%.

Platelet Factor 4 Detection. Human plasma and serum samples were also tested for the platelet-specific α-granule protein PF4 using a commercially available radioimmunoassay (Abbott Laboratories, Inc., North Chicago, IL). Serum was diluted 1:100 and plasma was not diluted before assaying.

Statistical Methods. Data were collected concerning the sex and age of the cancer patient or control individual, as well as the elapsed time from blood collection until centrifugation, PF4 concentration, and the PDGF-B concentration in both plasma and serum. Student’s t test was used to quantitate the effect of sex on the PDGF-B concentration. Pearson correlation analysis was used to identify any correlations between age, elapsed time from blood collection until centrifugation, and PF4 and PDGF-B concentrations in plasma and serum.

In addition, for the cancer patient group, data were collected concerning the platelet count and then correlated with all other data collected. Analysis of variance was used to test the effect of tumor cell type (epithelial, lymphoma, melanoma, and sarcoma) or stage of disease (primary, local recurrence, or metastatic) upon the PDGF-B value. Also, for the cancer patient group, the t test based on the externally studentized residuals was used to detect outliers in the PDGF-B, PF4 paired values. Outliers were removed and a regression line and 95% prediction limits surrounding the line were constructed. All statistical tests were conducted using the Statistical Analysis System (23), and a P value of 0.05 or less was accepted as statistically significant.

RESULTS

The double antibody sandwich ELISA used in these experiments could reliably detect the presence of rPDGF-BB >0.1 ng/ml (Fig. 1). When rPDGF-BB standards were spiked into control plasma, a curve parallel to that obtained with the standard curve in the linear regression range was obtained (Fig. 2). This result indicates that plasma PDGF-binding proteins, such as α2-macroglobulin (24), do not interfere with rPDGF-BB detection in the ELISA. We next tested plasma that was anticoagulated with either citrate, EDTA, or heparin, in the PDGF-B ELISA. Citrated plasma consistently yielded the lowest PDGF-B level for the control plasma and was used in all subsequent plasma collections. There was no cross-reactivity in the PDGF-B ELISA with epidermal growth factor (1 μg/ml), basic fibroblast growth factor (100 ng/ml), transforming growth factor-β (100 ng/ml), or homodimeric A-chain rPDGF (100 ng/ml) (data not shown).
The plasma PDGF-B level obtained from 72 healthy control individuals was 0.32 ± 0.14 ng/ml and ranged from 0.10 to 0.69 ng/ml (Fig. 3). Serum samples from 39 of the control individuals were also tested in the PDGF-B ELISA and yielded 10.56 ± 3.68 ng/ml and ranged from 3.92 to 20.29 ng/ml, showing the strong reactivity of the anti-rPDGF-BB antibody to human platelet PDGF. The mean PDGF-B levels in human serum are, therefore, >30-fold higher than plasma levels and reflect the occurrence of platelet α-granule release during serum preparation.

The control plasma and serum samples were also assayed for PF4, a platelet-specific protein that is a sensitive indicator of platelet α-granule release (25). The citrate plasma PF4 level in 68 controls was 97 ± 70 ng/ml, with a range of 34–363 ng/ml. The mean plasma PF4 level for controls reported here is 68 controls was 97 ± 70 ng/ml, with a range of 34-363 ng/ml. Therefore, it appears that a small amount of platelet α-granule release may have occurred in vitro during the preparation of platelet-poor plasma. Correlation analysis of the data for the control group supports this possibility since plasma PDGF-B levels did not correlate with the age \( r = -0.26 \) or sex \( P = 0.22 \) of the individual or the elapsed time between blood collection and centrifugation \( r = -0.11 \) but did show a substantial trend toward significance when compared to plasma PF4 \( P = 0.058 \) (Fig. 4) and serum PDGF-B \( P = 0.068 \).

To fully assess the extent of in vitro α-granule release from the control blood samples, blood from another group of 20 healthy controls was drawn with strict precautions to minimize in vitro platelet release (26), including the addition of prostaglandin E1 (final concentration, 100 ng/ml) and theophylline (final concentration, 180 μg/ml) to the EDTA-containing tubes used in blood collection. The plasma PDGF-B level in this control group was 0.11 ± 0.05 ng/ml, with a range of 0.06–0.29 ng/ml, and the PF4 level was 6.9 ± 1.9 ng/ml with a range of 4–13 ng/ml. These values are significantly lower than the 0.32 ± 0.14 ng/ml PDGF-B and 97 ± 70 ng/ml PF4 values obtained for the control group of 72 individuals whose blood was collected in citrate only and indicate that a small amount of in vitro platelet release did occur in the plasma samples of these controls. However, the citrate plasmaserum ratio of PDGF-B (3.0%) and PF4 (1.5%) indicate that this release was minimal when compared to serum values.

The plasma PDGF-B levels obtained from 131 cancer patients were grouped according to tumor type and are also shown in Fig. 3. For the total group of cancer patients, 19 of 131 (15%) had plasma PDGF-B levels greater than that of the highest control value (0.69 ng/ml) (Table 1). These elevated plasma PDGF-B levels were unaffected by the coincubation of rabbit IgG with the plasma in the ELISA. There were no significant differences in the plasma PDGF-B levels (Table 1), plasma PF4 levels, elapsed time between blood collection and centrifugation, or age of patient when these variables were compared within tumor-type subgroups by using analysis of variance. There were also no significant differences in these same variables when compared to the tumor stage (primary, local recurrence, or metastatic) of the patient. There was no correlation between plasma PDGF-B levels and the age \( r = 0.03, P = 0.77 \) or sex \( P = 0.49 \) of the patient.

There was, however, a significant correlation between plasma PDGF-B and plasma PF4 levels \( r = 0.31, P < 0.002 \) in the cancer patients (Fig. 5). Two cancer patients had elevated plasma PDGF-B levels that were found to be outliers on the basis of their externally studentized residuals. With these outliers removed, a regression line and 95% prediction limits surrounding the regression line were constructed (Fig. 5). Data points included within the 95% prediction limits represent plasma PDGF-B levels that are consistent with a platelet source of this factor, similar to the direct relationship of serum PF4 and platelet count that has been reported (25). For our cancer patient group, there was also a significant correlation between plasma PF4 levels and platelet count \( P < 0.02 \). Of the 131 cancer patients, 13 had PDGF-B levels that were higher than the highest control value but were within the 95% prediction limits, which is consistent with a platelet source for the elevated plasma PDGF-B levels in this group of patients. (Fig. 5).

Most interesting, however, was the group of patients with elevated plasma PDGF-B levels but low enough PF4 plasma levels to be >95% prediction limits of the PDGF-B, PF4 regression line (Fig. 5). Within this group of 6 patients, all except patient 3 had elevated plasma PDGF-B levels and PF4 levels within those of the control group (Table 2). This group of 5 of 131 cancer patients (4%) represents those who may have elevated nonplatelet sources of plasma PDGF-B.

When classification was done according to tumor type, there was no apparent correlation between the frequency of elevated nonplatelet plasma PDGF-B levels and the tumor type (Table 1). There was no apparent correlation between plasma PDGF-B level and the stage of disease for these 5 patients (Table 2).
ELEVATED PLASMA PDGF-B IN CANCER PATIENTS

Fig. 3. PDGF-B levels in citrate plasma from 72 control individuals and 131 cancer patients grouped according to tumor type. Dotted line, highest plasma PDGF-B level from the control group.

Fig. 4. Citrate plasma levels of PDGF-B and PF4 in the control group. Plasma PF4 levels were determined by radioimmunoassay. Both plasma PDGF-B and PF4 levels were available from 68 control individuals.

DISCUSSION

The development of a specific ELISA for the B-chain of PDGF that is described in this report has permitted the comparison of circulating levels of this growth factor in normal individuals and in cancer patients. This study establishes the mean concentration of PDGF-B in normal human citrated platelet-poor plasma at 0.32 ± 0.14 ng/ml. The mean PDGF-B concentration in human serum was 10.56 ± 3.68 ng/ml. Previous studies using a radioreceptor assay have reported normal human plasma and serum PDGF values of 1.0 and 15 ng/ml (27) and 0.2 and 17.5 ng/ml (28), respectively.

Determination of both the PDGF-B and PF4 levels of the cancer patient plasma allowed for the division of the cancer patients into three groups. PF4 is ideal to assay along with PDGF since PF4 is a platelet-specific peptide, and both peptides have almost identically rapid clearance times in plasma in vivo ($t_{1/2} < 2$ min) (28). The first group includes the majority of cancer patients (85%) who have normal plasma levels of PDGF-B.

The second group of patients includes those who have elevated plasma levels of both PDGF-B and PF4 (11%); the elevation of plasma PDGF-B may be due solely to platelet activation and release, either in vivo or in vitro, in this patient group. A previous study reported elevated levels of PF4 in some cancer patients (26); this platelet activation and release could possibly be due to low grade disseminated intravascular coagulation or platelet-tumor cell interaction. The third and most interesting group comprises those patients who had elevated...
### Table 1 Elevated plasma PDGF-B levels according to tumor type

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Total</th>
<th>Epithelial</th>
<th>Sarcoma</th>
<th>Melanoma</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer patients with elevated plasma PDGF-B^4</td>
<td>19/131 (15)^*</td>
<td>10/84 (12)</td>
<td>5/24 (21)</td>
<td>1/9 (11)</td>
<td>3/14 (21)</td>
</tr>
<tr>
<td>Cancer patients with elevated plasma PDGF-B and control levels of plasma PF4^4</td>
<td>5/131 (4)</td>
<td>3/84 (4)</td>
<td>1/24 (4)</td>
<td>0/9 (0)</td>
<td>1/14 (7)</td>
</tr>
</tbody>
</table>

^4 Elevated plasma PDGF-B values were all above the highest control level of 0.69 ng/ml.
^* Ratio of elevated plasma PDGF-B values to the total; numbers in parentheses, percentage.
^1 PDGF-B levels were all >0.69 ng/ml, and plasma PF4 levels were below the highest control value of 363 ng/ml.

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Fig. 5. Citrate plasma levels of PDGF-B and PF4 in the cancer patient group. Both plasma PDGF-B and PF4 levels were available from 98 cancer patients.

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### Table 2 Elevated plasma PDGF-B chain levels in cancer patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Plasma PDGF-B (ng/ml)</th>
<th>Plasma PF4 (ng/ml)</th>
<th>Diagnosis</th>
<th>Stage of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.20</td>
<td>5.96</td>
<td>Osteogenic sarcoma</td>
<td>Metastatic to lung</td>
</tr>
<tr>
<td>2</td>
<td>2.10</td>
<td>230</td>
<td>Lymphocytic lymphoma</td>
<td>Primary: stage IA (orbital only)</td>
</tr>
<tr>
<td>3</td>
<td>1.75</td>
<td>657</td>
<td>Esophageal adenocarcinoma</td>
<td>Metastatic to liver, lung</td>
</tr>
<tr>
<td>4</td>
<td>1.57</td>
<td>59</td>
<td>Rectal adenocarcinoma</td>
<td>Metastatic to bone, soft tissue</td>
</tr>
<tr>
<td>5</td>
<td>1.51</td>
<td>87</td>
<td>Endometrial adenocarcinoma</td>
<td>Primary: stage I, grade II</td>
</tr>
<tr>
<td>6</td>
<td>0.89</td>
<td>74</td>
<td>Rectal adenocarcinoma</td>
<td>Metastatic to liver</td>
</tr>
</tbody>
</table>

Controls
Mean ± SD 0.32 ± 0.14 97 ± 70
Range 0.10–0.69 34–363
n 72 68

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plasma PDGF-B and plasma PF4 levels similar to those of the control group. In these patients a nonplatelet source of PDGF-B is probable.

The elevated plasma PDGF-B levels detected in this last group of patients could be tumor-derived. If this is the case, an autocrine mechanism may be operative in the patient with osteosarcoma. This patient had a plasma PDGF-B value of >5 ng/ml, which is more than 15-fold higher than the mean plasma level for controls. This value is also within the serum range for PDGF-B in normal controls and is far above the published half-maximal activity of PDGF for mitogenesis of mesenchymal cells: 0.3 ng/ml for human fibroblasts (29), 1 ng/ml for Swiss 3T3 cells, and 0.9–6.0 ng/ml for smooth muscle cells (30). PDGF receptors should be present on these tumor cells since they are of mesenchymal origin, and if the tumor cells secrete PDGF, as has been shown for many tumor cells in culture (13–15, 31), then an autocrine loop could be formed.

In the other four patients with elevated plasma PDGF-B but control PF4 levels, 3 had epithelial tumors and one had lymphocytic lymphoma. Except in extremely rare cases (32, 33) these cell types do not possess PDGF receptors and, therefore, would not be growth stimulated in an autocrine fashion by PDGF. The production of PDGF by these tumor cell types could be an epiphenomena unrelated to transformation or it could be important for the paracrine growth of neighboring mesenchymal cells.

There may be several reasons why nonplatelet PDGF was elevated in only a small proportion (4%) of cancer patients. The PDGF-B ELISA which we developed binds only PDGF-B; since the A- and B-chains of PDGF are independently regulated, there may be elevations of PDGF-A that have gone undetected. Second, the local production and biological effects of PDGF in the tumor may sometimes occur without elevating the plasma level, due in part to dilution in the total blood
volume and to the short half-life of PDGF in the circulation (28). Third, PDGF is only one of a growing group of growth factors and oncogenes which when activated may cause cancer.

It is presumed that the tumor cells are producing the elevated plasma PDGF-B levels reported here, but it is possible that normal host tissues are the source of this PDGF. Experiments utilizing immunohistochemistry are needed to further determine the source of the elevated plasma PDGF-B levels. In conclusion, plasma PDGF-B level deserves further study as a tumor marker in certain cancer patients.

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