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RESEARCH

Plasma Levels of Phospholipase A_2-IIA in Patients with Different Types of Malignancies: Prognosis and Association with Inflammatory and Coagulation Biomarkers

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Abstract It is well-known that the plasma level of group IIA phospholipase A_2 ($sPLA_2$-IIA) is increased in patients with malignant diseases, but whether the up-regulated enzyme expression is directly related to tumorigenesis or a consequence of tumor-associated inflammation remains unresolved. In this study we analyzed circulating levels of $sPLA_2$-IIA, C-reactive protein (CRP), fibrinogen, factor VIII (FVIII), von Willebrand factor (vWF), and antithrombin as biomarkers of inflammation and coagulation in patients with various types of malignancies. Underlying tumor entities were lung, esophageal, gastric, pancreatic, colorectal, head and neck, and hepatocellular carcinomas as well as multiple myeloma and non-Hodgkin's lymphoma. Plasma levels of $sPLA_2$-IIA are shown to be markedly increased in all types of analysed malignancies in comparison to the normal range (22.8±4.5 μg/L versus <1.9 μg/L). Levels of $sPLA_2$-IIA correlate positively with CRP ($p<0.001$), fibrinogen ($p<0.01$), FVIII ($p<0.05$), and vWF ($p<0.05$) and negatively with antithrombin levels ($p<0.05$). Kaplan-Meier analyses revealed a statistically prolonged survival time of patients with lower $sPLA_2$-IIA concentrations (<4 μg/L) in comparison to those with elevated concentrations (>4 μg/L) of this enzyme. In conclusion, the study shows that the measurement of plasma $sPLA_2$-IIA levels has prognostic values in patients with different types of malignancies. The association of $sPLA_2$-IIA levels with CRP, fibrinogen, FVIII, and vWF levels supports the importance of inflammatory processes for the up-regulation of $sPLA_2$-IIA during cancer progression.

Keywords Cancer · Inflammation · Secreted phospholipase A_2 · C-reactive protein · Fibrinogen

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Introduction

Secreted phospholipase A_2 type IIA ($sPLA_2$-IIA) is classified as an acute phase reactant and markedly increased not only during inflammatory disorders, but also in malignant diseases [1–3]. Up-regulated expression of $sPLA_2$-IIA was revealed at tissue levels in specimens obtained from different types of cancers suggesting a direct involvement of this enzyme in tumorigenesis [3–7]. In line with this conclusion is the observation that high concentrations of $sPLA_2$-IIA can be measured in blood samples of patients with advanced and metastasized cancers in comparison to those with early cancers [3, 8–11]. On the basis of these data it was suggested that $sPLA_2$-IIA is secreted by cancer cells into the circulation and that the measurement of the enzyme concentration may help to distinguish between aggressive and indolent cancers and benign forms [10, 11]. However, not all data are consistent in the usage of serum $sPLA_2$-IIA levels as reliable biomarker in the diagnosis of malignancies. There is some evidence that

liver cells, but not blood or cancer cells are the main source of increased blood levels of $sPLA_2$-IIA during inflammation and carcinogenesis [12–14]. In addition, decreased expressions of PLA_2-IIA were described in metastatic carcinomas compared to those in primary carcinomas [4]. The latter finding disagrees with the reported increase of $sPLA_2$-IIA in serum of patients with advanced cancer relative to early cancer [3, 8–11]. Moreover, inflammatory and allergic diseases may result in elevated serum levels of $sPLA_2$-IIA, emphasizing the role of this enzyme as an acute phase reactant during inflammatory reactions of carcinogenesis [1, 2, 15].

A link between inflammation and increased risk of cancer development is well established [for reviews 16, 17]. Distinct malignancies such as cervical and hepatocellular carcinoma, Kaposi's sarcoma, or gastric cancers are thought to arise secondary from chronic inflammation [18]. Inflammation-based biomarkers and prognostic scores enable not only the identification of patients at risk, but also provide well-defined therapeutic targets for future clinical trials [19]. During acute and chronic inflammatory diseases, levels of $sPLA_2$-IIA increase simultaneously to C-reactive protein (CRP) [12]. Similar to $sPLA_2$-IIA, increased CRP levels are considered as risk factor for cancer progression. The usage of CRP as additional predictor of survival and post-treatment monitoring was shown in multiple myeloma, melanoma, lymphoma, ovarian, renal, pancreatic, prostatic and gastrointestinal tumors [20, 21]. Fibrinogen and factor VIII are also acute-phase reactants and belong to important determinants of the metastatic potential of tumor cells [22–24]. For example, low levels of fibrinogen reduced the development of lung metastases in xenograft mice with Lewis lung carcinoma and B16 melanoma lines [25].

To analyse the prognostic potency of $sPLA_2$-IIA as biomarker for cancer progression we measured the concentrations of this enzyme in addition to CRP, fibrinogen, FVIII, von Willebrand factor (vWF), and antithrombin in plasma samples of patients with different types of malignancies.

Table 1 Patient characteristics

Characteristics	Cases	Pathological stage of PT	Histological type of PT
Median age (range), years	60 (18–80)		
Sex, male/female	55/18		
Total number of cancer patients	73		
Patients receiving anti-infective and NSAID medications	43 (58.9 %)		
Solid cancers	58		
Lung	13	I, II (15.4 %) III, IV (84.6 %)	NSC adeno-Ca (46.2 %); SC adeno-Ca (38.5 %); others (15.3 %)
Esophageal	9	II (11.1 %) III, IV (88.9 %)	adeno-Ca (33.3 %); squamous cell-Ca (66.7 %)
Gastric	8	II (25.0 %) III, IV (75.0 %)	adeno-Ca (100.0 %)
Pancreatic	8	I (12.5 %) III, IV (87.5 %)	adeno-Ca (87.5 %); others (12.5 %)
HCC	4	Okuda stage I (75 %) Okuda stage II (25 %)	
Colorectal	5	III, IV (100.0 %)	adeno-Ca (100.0 %)
Head and neck cancers	4	IV (100 %)	squamous cell-Ca (25.0 %); others (75.0 %)
Others	7	CUP (28.6 %) III, IV (81.4 %)	
Hematologic malignancies	15		
Multiple myeloma	6	III, IV (100 %)	
Non-Hodgkin's lymphoma	9	III, IV (100 %)	low malignant (33.3 %); high malignant (66.7 %)

PT primary tumor, *HCC* hepatocellular carcinoma, *NSC* non-small cell, *SC* small cell, *adeno-Ca* adenocarcinoma, *CUP-syndrome* carcinoma of unknown primary

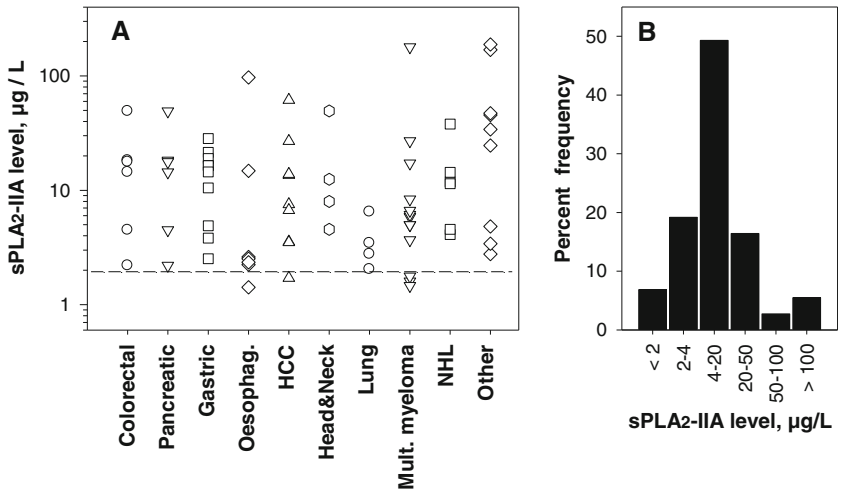

Fig. 1 Concentrations of $sPLA_2$-IIA in plasma samples of patients with malignancies. **a** Scatter plot of $sPLA_2$-IIA levels in plasma samples of patients with different kinds of cancers. *Dots* represent the average of duplicate analyses for each patient and the *dotted line* shows the normal range of $sPLA_2$-IIA with <1.9 µg/L. **b** Histogram representing the distribution of $sPLA_2$-IIA concentrations in plasma samples of cancer patients

Patients and Methods

Patients

A total of 73 hospitalized patients with malignant disorders were included into the study. The patient characteristics are shown in Table 1. Among 58 patients with solid cancers, 13 patients had lung, 9 esophageal, 8 gastric, 8 pancreatic, 4 hepatocellular, 5 colorectal cancers, 4 head and neck cancers and 7 patients had other solid tumors including patients suffering from CUP-syndrome (carcinoma of unknown primary), renal cell carcinoma, sarcoma, germ cell tumor and endometrial cancer. Hematologic malignancies were diagnosed in 6 patients as multiple myeloma and in 9 patients as non-Hodgkin's lymphoma. The current status of all enrolled patients was monitored up to 40 months after the beginning of the study. In comparison to cancer patients 50 plasma samples of age-matched healthy individuals (the mean age of the control group was 59.1±11.1 years) were analysed.

The ethic-committee of the Medical Faculty of the TU-Dresden agreed to conduct the study (EK 187 112 000).

Biochemical and Clinical Analyses

Blood samples were collected from peripheral veins in a syringe filled with citrate as described earlier [26]. Plasma samples were obtained by centrifugation and frozen at −80° C for subsequent analysis. Plasma concentrations of $sPLA_2$-IIA were measured using an ELISA kit (Cayman Chemical, MI, USA) according to the manufacturer's protocol. Human plasma samples were diluted 10 times for ELISA analyses and the extinction of reaction products was measured at 405 nm on Victor3 1420 Multilabel Counter reader (Perkin-Elmer LAS GmbH, Germany). Amounts of $sPLA_2$-IIA tested in duplicate were calculated using standards included in the ELISA kit and software supplied with Victor3. Plasma levels of CRP, fibrinogen, von Willebrand factor antigen, factor VIII activity, and antithrombin III were analyzed using Tina-quant C-reactive protein gen. 3 (CRPL3), STA fibrinogen, STA LIA test vWF, STA factor VIII, and STA antithrombin III (Roche Diagnostics, Mannheim, Germany), respectively.

Statistical Analyses

All statistical analyses were performed using a statistic module integrated into the SigmaPlot11 software (Systat Software GmbH, Erkrath, Germany). The strength of a stochastic relationship between two variables was analyzed using correlation calculations and determination of the Pearson correlation coefficient *r*. Group comparisons for unpaired samples were performed using the *U*-test according to Mann and Whitney. Survival curves were created by the method of Kaplan and Meier. Differences were considered significant at $p<0.05$.

Table 2 Plasma levels of inflammation- and coagulation-related plasma proteins in patients with malignancies

Biomarker	Units	Normal range	Mean	SD	SEM	Median (range)
$sPLA_2$-IIA	µg/L	<1.9[a]	22.8	38.6	4.5	8.3 (1.4–188.7)
CRP	mg/L	<5.0[b]	46.8	56.7	5.8	22.1 (0.1–291.3)
Fibrinogen	g/L	1.5–4.5[b]	5.8	1.9	0.2	5.6 (2.0–10.6)
F VIII	%	70–140[b]	188.5	50.0	5.0	186 (94–300)
vWF	%	50–160[b]	280.0	146.0	14.6	243 (62–784)
Antithrombin	%	80–120[b]	97.6	21.3	2.1	99 (49–142)

[a]Calculated from the 95th percentile of the $sPLA_2$-IIA values in plasma samples of healthy individuals (N=50); [b]Normal range according to manufacturer's data

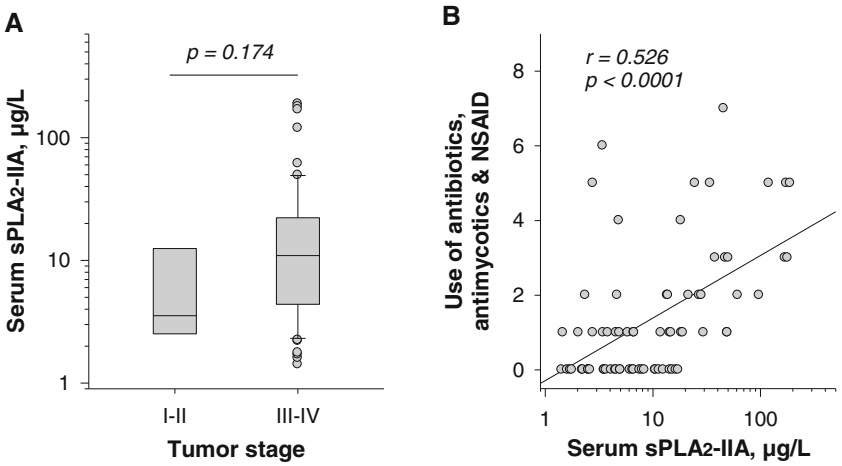

Fig. 2 Plasma levels of $sPLA_2$-IIA in relation to tumor stage (**a**) and the use of anti-infective and NSAID medications (**b**) in cancer patients. **a** Box-plots of $sPLA_2$-IIA plasma levels of patients with tumor stages I-II and III-IV. *Boxes within the plots* represent the 25-75th percentiles. Median values are depicted as *solid lines*. *Circles* indicate outlier values outside of the 10th and 90th percentiles. Statistical difference between both groups was calculated by Mann–Whitney rank sum test. **b** Scatter plots for Pearson correlation analyses of plasma levels of $sPLA_2$-IIA versus the application of anti-infective and anti-inflammatory medications; *r*, Pearson correlation coefficient. The application of anti-infective and NSAID medications (number of prescriptions) were computed for each patient

Results

Increased Plasma Levels of $sPLA_2$-IIA in Patients with Malignancies

Plasma levels of $sPLA_2$-IIA are increased in 68 of 73 analysed samples of patients with malignancies compared with healthy individuals (<1.9 μg/L) (Fig. 1a). The median value of $sPLA_2$-IIA was 8.3 μg/L, with minimum and maximum values at 1.4 and 188.7 μg/L (Table 2). The distribution of the plasma levels of $sPLA_2$-IIA within the cancer patients has a peak in the moderately elevated group of 4–20 μg/L (Fig. 1b). Mann–Whitney rank sum test revealed no significant difference between serum levels of $sPLA_2$-IIA in patients with stage I-II of primary tumor and patients with stage III-IV (Fig. 2a). The analysis of $sPLA_2$-IIA plasma concentrations of patients and their relationships to the use of anti-infective and NSAID medications demonstrated a high significant correlation (r=0.526, Fig. 2b).

Correlation of $sPLA_2$-IIA Plasma Concentrations with CRP, Fibrinogen, FVIII, and vWF Concentrations in Cancer Patients

Similar to $sPLA_2$-IIA, the mean CRP level (42.9±5.8 mg/L) is strongly increased in cancer patients in comparison to the normal range of CRP (<5.0 mg/L, Table 2). The same is true for fibrinogen (5.8±0.2, normal range: 1.5–4.5 g/L), vWF (188.5±50.0 % normal range: 70–140 %) and factor VIII (280±146 % normal range: 50–160 %, Table 2). In case of antithrombin, 15 patients had plasma levels below 80 % and 9 had plasma levels above 120 % as normal limits. Other cancer patients had plasma levels within the normal range of 80–120 % (Table 2).

Table 3 Pearson correlation coefficients for relationships observed between $sPLA_2$-IIA and biomarkers of inflammation and coagulation in plasma samples of patients with malignancies

	$sPLA_2$-IIA	CRP	Fibrinogen	vWF	F VIII	AT
$sPLA_2$-IIA	–	0.492**	0.271*	0.276*	0.245*	−0.285*
CRP	0.492**	–	0.510**	0.225*	0.310*	−0.334**
Fibrinogen	0.271*	0.510**	–	ns	0.353**	ns
vWF	0.276*	0.225*	ns	–	0.340*	ns
Factor VIII	0.245*	0.310*	0.353**	0.340*	–	ns
AT	−0.285*	−0.334**	ns	ns	ns	–

ns not significant, *AT* antithrombin, *vWF* von Willebrand factor

Correlations of different pairs of variables were studied using Pearson correlation test. Significance of correlation: * p<0.05; ** p<0.001

By using Pearson test it is shown that plasma levels of $sPLA_2$-IIA and CRP (r=0.492) as well as fibrinogen and CRP (r=0.510) are significantly associated (Table 3). Plasma $sPLA_2$-IIA levels also correlate with fibrinogen, FVIII, and vWF, although the correlations are weaker (Table 2). In contrast, the levels of antithrombin of cancer patients are negatively correlated with CRP (r=−0.334) and $sPLA_2$-IIA (r=−0.285) and do not correlate with the other analyzed plasma biomarkers (Table 3).

On the basis of $sPLA_2$-IIA plasma levels, cancer patients were classified into three groups having $sPLA_2$-IIA concentrations <4 μg/L (group-1, N=19); 4–20 μg/L (group-2, N=36), and >20 μg/L (group-3, N=18). According to this classification, levels of CRP, fibrinogen, FVIII, vWF, and antithrombin are significantly different between group-3 and group-1 of patients (Fig. 3). In cases of CRP and fibrinogen, differences are also significant between group-2 and group-1.

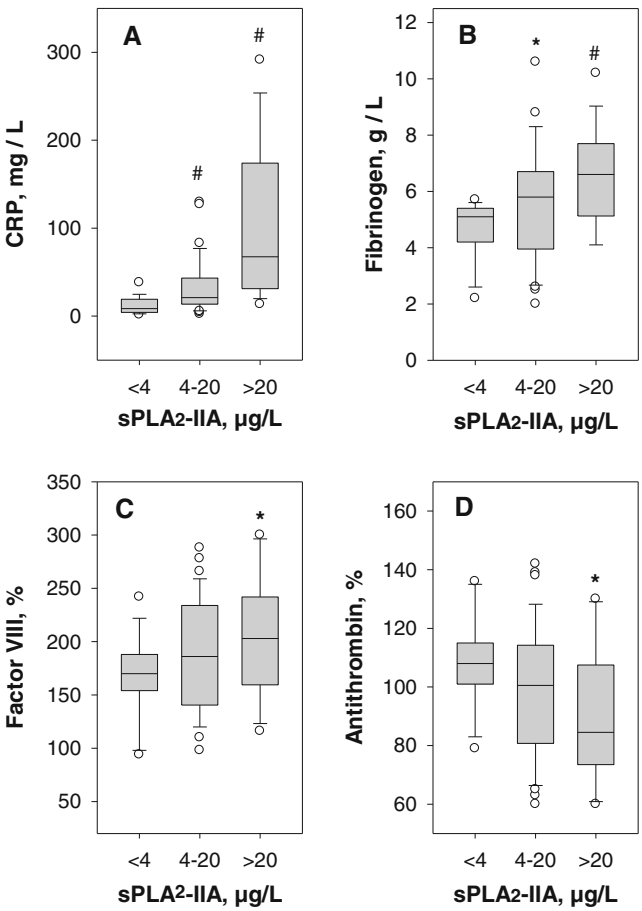

Fig. 3 Plasma levels of CRP, fibrinogen, factor VIII, and antithrombin in cancer patients with increasing concentrations of $sPLA_2$-IIA. Boxplots of plasma levels of CRP (**a**), fibrinogen (**b**), factor VIII (**c**) and antithrombin (**d**) in cancer patients classified into three groups relative to plasma levels of $sPLA_2$-IIA. Statistical differences relative to group-1 with low $sPLA_2$-IIA levels were calculated by Mann–Whitney rank sum test. * p<0.05 and # p<0.001

Survival Analysis

During a 40-months follow-up, 76 % of the cancer patients died. Retrospectively, a prognostic value of $sPLA_2$-IIA plasma levels was found using Kaplan-Meier analyses. Data reveal a highly significant survival difference between patients of group-2 and group-3 in relation to those of group-1 (p=0.001 and p=0.0062, respectively, Fig. 4).

Discussion

The present study shows that patients with malignant diseases have increased plasma levels of $sPLA_2$-IIA. Similar to CRP, fibrinogen, FVIII, and vWF whose plasma concentrations are also elevated in cancer patients, $sPLA_2$-IIA can be classified as an acute-phase protein. Therefore, these data emphasize the link between cancer and inflammation which has been intensively discussed during the last decade [23–28]. Further evidence for this link is given by the fact that systemic inflammations are evident at the earliest stages of neoplastic progression [29, 30]. Furthermore, it is known that inflammation may force the tendency of cancers to metastasize and may influence the ability of patients to tolerate anticancer therapy [18]. In a previous study on patients with prostate cancers we found increased blood levels of $sPLA_2$-II in localized prostate cancers without metastases but also in benign prostatic hyperplasia [31]. Serum levels of $sPLA_2$-IIA correlated with concentrations of CRP, but not with PSA, Gleason score, or tumor stage.

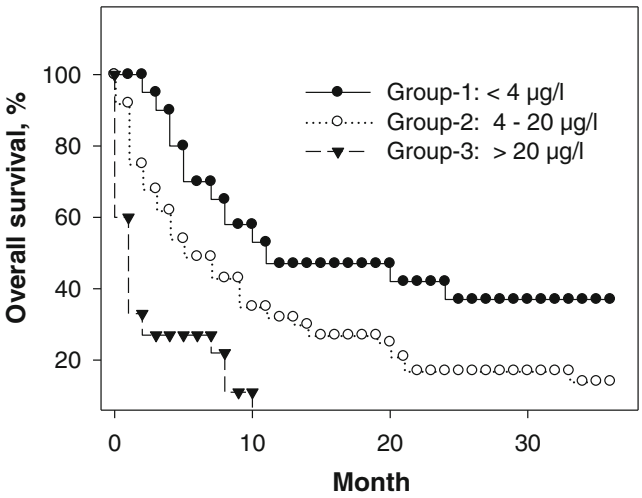

Fig. 4 Plasma levels of $sPLA_2$-IIA in patients with malignancies as predictor of survival in Kaplan–Meier analyses. Patients with cancers were classified into three groups according to the plasma level of $sPLA_2$-IIA: group-1 (< 4 μg/L, N=19 patients); group-2 (4–20 μg/L, N=36 patients); and group-3 (> 20 μg/L, N=18 patients). Log-Rank test: group-1 *vs* group-2: p=0.3434; group-1 *vs* group-3: p=0.0014; group-2 vs group-3: p=0.0032

This finding emphasized the role of inflammatory processes both in BPH and prostate cancer.

The data of this study are in line with previous studies showing that increased concentrations of $sPLA_2$-IIA strongly correlated with CRP levels in serum of patients with acute and chronic inflammatory diseases as well as with malignancy [12, 31, 32]. According to current concepts, the tumorigenesis is mediated by over-activation of oncogenic signaling and inactivation of tumor-suppressive pathways (for review [29, 30]). In this context, transcription factors such as STAT3 and NF-κB play a crucial role [33, 34]. Recent findings underscore the NF-κB signaling pathway as a promising target for cancer prevention and treatment [35]. It is known that the up-regulation of $sPLA_2$-IIA, CRP, and FVIII expressions is closely related to the activation of NF-κB [1, 21, 36, 37]. The central role of this transcription factor in immediate early gene activation during inflammation and tumorigenesis may explain not only the positive relationships between $sPLA_2$-IIA and other inflammatory biomarkers, but also the negative correlation with antithrombin. The major inhibitor of thrombin in plasma exhibits anti-inflammation activity and exerts positive effects in sepsis, possible due to a negative feedback on the activation of NF-κB by antithrombin [38, 39]. In line with this is the observation that the inhibition of NF-κB-related signaling pathways underlies the suppressive effect of antithrombin on $sPLA_2$-IIA expression in endothelial cells [40]. In contrast to antithrombin, fibrinogen activates NF-κB and mediates inflammatory reactions [41, 42]. Fibrinogen itself is efficiently induced by interleukin-6 (IL-6) and STAT3 was shown to be required for the IL-6 mediated up-regulation of this gene in the course of inflammation [43].

An additional finding of the current study is the correlation between plasma concentrations of $sPLA_2$-IIA and the overall survival rates of patients with malignant diseases. Patients with high levels of plasma $sPLA_2$-IIA (>20 μg/L) showed a significantly shorter survival toward patients with low levels of plasma $sPLA_2$-IIA (<4 μg/L). In agreement with this correlation are previous data showing a relationship between the $sPLA_2$-IIA expression in prostate tissues and the stage of prostate malignancies [44–47]. For example, a poor 5-year-survival rate of patients with prostate malignancies was described in case of increased $sPLA_2$-IIA expression [44]. The correlation between the shorter survival of patients with increased plasma $sPLA_2$-IIA levels may be associated with infectious complications during cancer progression [48]. The data of this study demonstrating a significant correlation between $sPLA_2$-IIA plasma levels and the use of anti-infective and NSAID medications are consistent with this conclusion.

Another study emphasized the role of $sPLA_2$-IIA as a negative prognostic determinant in stage II colorectal carcinoma and prostatic cancer, but not in case of pancreatic cancer [44, 49]. Although elevated $sPLA_2$-IIA expressions were also described in primary gastric, colon, and prostrate early-stage tumors, a decreased expression of $sPLA_2$-IIA was identified in metastatic and late-stage tumors [50]. These inconsistent results may be probably attributed to interaction of cancer with microenvironment and divergent genetic pathways present in different malignant tissues [51]. A strong association between down-regulation of $sPLA_2$-IIA and promoter methylation of this gene was described in gastric cancer cells suggesting that the loss of $sPLA_2$-IIA expression in late-stage cancers may be due to epigenetic silencing [50]. A similar hypermethylation of the *PLA2G2A* gene we identified in $sPLA_2$-IIA-negative prostate cancer DU-145 cells as well as in U937 and Jurkat leukemic cell lines [52, 53].

In conclusion, this study supports the crucial role of inflammation in the process of tumorigenesis. Plasma concentrations of $sPLA_2$-IIA and other acute phase reactants such as CRP, fibrinogen, FVIII, and vWF are increased in patients with different types of malignancies. The up-regulation of $sPLA_2$-IIA is associated with a poor survival of patients and is not limited to specific cancer type. Therefore, the measurement of $sPLA_2$-IIA levels in circulation may be helpful for the prognosis of malignant diseases and optimization of cancer patient therapies.

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