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CD26/DPPIV cell membrane expression and DPPIV activity in plasma of patients with acute leukemia

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Abstract

CD26/DPPIV (dipeptidil peptidase IV) displays an array of diverse functional properties, with a role in the development of several human cancers. This enzyme is found mainly anchored in the membrane of cells although it also has an enzymatically active plasma isoform. The regulation of biological activities of cytokines by DPP IV activity has a potential role in the homeostatic regulation of hematopoiesis. In this study, we analyzed the CD26 antigen cell membrane expression by flow cytometry and the DPPIV activity in plasma of patients of acute leukemia. The results showed that the plasma DPPIV activity is significantly higher in leukemia patients and could be 100% inhibited by Januvia™ (Merck Sharp & Dohme) a selective DPPIV inhibitor. Although CD26 expression on immune cells were not leukemia-dependent the analysis of the correlation between CD26 expression and the DPPIV plasma activity were statistically significant ($p < 0.01$) in acute lymphoid leukemia (B-ALL and T-ALL).

Keywords: *CD26, DPPIV, dipeptidyl peptidase, leukemia, immunophenotype, sitagliptin, inhibition*

Introduction

CD26/DPPIV, dipeptidyl peptidase IV (DPPIV, EC 3.4.14.5) has gained more importance in the research fields of biology and medicine [1,2] due to its ability to process a variety of peptides [3] including several cytokines [4,5], chemokines [6–8], neuropeptides [9], and peptide hormones [10–16]. The enzyme typically releases dipeptides from N-terminus of peptides with proline or alanine in the penultimate position and this might result in activation, inactivation or in modulation of the peptide's activities [7,11,16]. The CD26/DPPIV is expressed preferentially anchored in the membrane of cells from different tissues, e.g. liver, intestine, kidney, mature thymocitos, T cells, B cells, NK cells and macrophages [17–19]. DPPIV/CD26 has also an enzymatically active plasma soluble counterpart probably originated from T-cells [20]. In addition to its enzymatic activity, interactions of CD26/DPPIV with molecules such CD45 and ADA have been described in the last decades, such interactions must be involved with signal transduction process and modulation of co-stimulation and proliferation of activated T lymphocytes [21–24]. CD26/DPPIV seems to mediate multiple, cell context specific functions in both benign and malignant tissues. Deregulations of its expression and enzymatic activity may contribute to cancer development either directly—on the level of the transformed cell itself—or

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indirectly, as an immunomodulator [25,26]. CD26/DPPIV was for many years believed to be a unique enzyme cleaving X-Pro dipeptides from the N-terminal end of peptides and proteins but in the last years a lot of isoenzymes with DPPIV activity or DPPIV structure homologues were discovered and clustered in a protein family designated as "DPPIV activity and/or structure homologues" (DASH) [27]. Inhibitors of DPPIV are expected to be of significant therapeutic value in the treatment of a lot of pathologies including diabetes mellitus, HIV infection, immunosuppressant in the transplantation surgery, autoimmune diseases and also cancer. However, the almost ubiquitous expression and multifunctional nature of the majority of DASH may complicate the prediction of the systemic consequences of their inhibition in general [27]. A highly selective DPPIV inhibitor sitagliptin phosphate (Januvia™) [28] has been found to demonstrate at least a 2600-fold margin over its activity against the closely related enzymes DPP-8 and DPP-9 [29]. This inhibitor is used in clinical treatment of diabetes mellitus as a selective DPPIV inhibitor.

The aim of the present study was to characterize the expression of CD26/DPPIV on immune cells and the plasma DPPIV activity in patients with acute leukemia and verify if the selective inhibitor of DPPIV sitagliptin is able to inhibit plasma DPPIV activity of patients with acute leukemias. This information could be very important even more so in times when the concept of DPPIV activity inhibition for therapeutic purposes has reached the stage of clinical application.

Material and methods

Samples

A total of 81 samples were analyzed in this study. They were obtained from 62 patients newly and consecutively diagnosed as acute leukemia. The control group was divided into 2 subgroups: (i) 9 samples without leukemia were from patients with other haematological alteration but without leukemia features and (ii) 10 samples from normal blood donor subjects. The mean age of the leukemia patients were 8 years for B-ALL, 11.5 years for T-ALL and 24 years for AML. The control groups mean age were 7.8 years for the non-leukemia patients and 24 years for the normal control group. Patients characteristics at diagnosis are summarized in Table I. The initial leukemia diagnostic was based on morphological aspects according standard criteria [30].

Table I. Sample characteristics.

Total number of patients	np/nt	%
Sex		
Male	44/81	54.3
Female	37/81	45.7
Leukocyte ($\times 10^3$)		
0-50	38/62	61.3
> 50	24/62	38.7
Leukemia subtypes and controls		
Bp-ALL	37/81	45.7
T-ALL	8/81	9.9
AML	17/81	21
Others*	9/81	11.1
Blood donors	10/81	12.3

*Non-leukemia cases were patients with others hematological alterations; np/nt = number of positive cases/number of cases tested.

Immunophenotyping of mononucleated cells

Immunophenotype was performed by direct immunofluorescence monoclonal antibodies (MoAb) on fresh leukemic cells of bone marrow (MO) aspirates and, analyzed by flow cytometry. For the diagnoses of leukemia the MoAb panel tested the intracytoplasmatic expression distributed as follows: a-MPO^{FITC}/$CD79a^{PE}$/$cCD3^{CY}$; $CD22^{PE}$/TdT^{FITC}; $cIg\mu^{FITC}$, $CD13^{PE}$. Then, the following membrane surface antigens expression were tested according to cell lineage positive in the previous analysis: (i) for B-cell lineage: $CD34^{FITC}$/$CD38^{PE}$/$CD19^{CY}$; $CD34^{FITC}$/$CD19^{PE}$/$CD45^{CY}$; $CD10^{FITC}$/$CD19^{PE}$/$CD45^{CY}$; $CD10^{FITC}$/$CD20^{PE}$/$CD19^{CY}$; (iii) for myeloid-lineage: $CD34^{FITC}$, $CD33 + 13^{PE}$/$CD45^{CY}$; $CD33^{FITC}$, $CD56^{PE}$/$CD45^{CY}$; $CD42a^{FITC}$, $CD41^{PE}$/$CD45^{CY}$, $CD33 + 13^{FITC}$, $CD19^{PE}$/$CD45^{CY}$, $CD33 + 13^{FITC}$, $CD7^{PE}$/$CD45^{CY}$; (ii) for T-cell: $CD34^{FITC}$/$CD38^{PE}$/$CD7^{CY}$; $CD2^{FITC}$/$CD5^{PE}$/$CD45^{CY}$; $CD2^{FITC}$, $CD7^{PE}$/$CD45^{CY}$; $CD16^{FITC}$/$CD56^{PE}$/$CD3^{CY}$; $CD33^{FITC}$/$CD7^{PE}$/$CD45^{CY}$, $CD2^{FITC}$/$CD10^{PE}$/$CD7^{CY}$; $CD2^{FITC}$/$CD1a^{PE}$/$CD7^{CY}$; $CD4^{FITC}$/$CD8^{PE}$/$CD7^{CY}$; $TCR\alpha/\beta^{FITC}$/$TCR\gamma/\delta^{PE}$/$CD3^{CY}$.

The percentages of the total number of cells expressing an antigen were considered positive when an antibody labeled 20% or more.

For the CD26/DPPIV membrane expression we used the following additional test $CD26^{FITC}$/$CD3^{PE}$.

The results of immunological classification of acute leukemia were based on criteria previously published by the *European Group for the Immunological Characterization of Leukemias*-EGIL [31].

Plasma fluids analysis

DPPIV enzyme activity assay. The enzyme activity was measured in plasma fluids collected previous to any treatment. 10 μL of plasma was mixed with 20 μL of the substrate solution (20 mM) Gly-Pro-p-nitroaniline (Sigma) in 0.1M Tris/HCl buffer pH 7.4, final volume 200 μL and incubated in a rotary shaker bath at 37°C for 1 h. The reaction was interrupted by adding 800 μL of 1 M sodium acetate buffer pH 4.4.

After centrifugation for 5 min at 10,000 × g, the absorbance of the supernatant was measured at 405 nm. The negative control of the reaction was prepared by adding sodium acetate buffer before the addition of substrate. Both the reactions and the control assays were carried out in triplicate. In order to determine the concentration of p-nitroaniline released by DPPIV activity a standard curve of p-nitroaniline (Sigma) was prepared with concentrations from 0.01 to 0.1 mM. The DPPIV enzyme activity is expressed in U/mg of total protein in plasma. One unit of DPPIV activity is defined as the enzyme activity that produces 1 nmol of p-nitroaniline/minute at 37°C and pH 7.4.

Protein quantification. The plasma protein quantifications were done by Kit DC protein assay (BioRad) according to manufacturer's protocol. The plasma was diluted (1:100) and 20 μL was used for protein quantification. The control of the reaction was done with 20 μL of water instead of plasma. All the reactions were done in triplicates.

DPPIV enzyme inhibition activity assay. The inhibition assay was carried out using the drug Januvia™ (sitagliptin phosphate) produced by Merck Sharp & Dohme that is commercially available. For both of Januvia™ a pill containing 100 mg of sitagliptin phosphate was scraped with a razor to withdraw the coating color. Then the pill was dissolved in 5 mL of Tris/HCl 0.1 M pH 7.4 buffer. The suspension was then centrifuged to 1000 × g for 5 min and 10 μL of supernatant were applied for the inhibition activity assay that was done exactly as described for the DPPIV enzyme activity assay except that 10 μL of the tris/HCl 0.1M pH 7.4 buffer was replaced by 10 μL of supernatant inhibitor solution.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 statistical software. Exploratory and univariated analysis were done. The univariate analysis included the qui-square test (categorical variables) and the Student's t-test (numeric variables). The $p < 0.05$ values were considered statistically significant.

Results and discussion

The main characteristics of subject and samples are shown in Table I. There were no statistical significance regarding age range and gender among the different types of acute leukemia and the control group. Overall, results of surface antigen expression according to CD26 presence versus CD26 absence in acute leukemia patients at diagnosis are listed in Table II. Among the 62 samples of acute leukemia cells tested, 66.1% were $CD26^{+ve}$ and 33.9% were $CD26^{-ve}$. No differences were observed in non-leukemia patients that showed 66.7% of the samples were $CD26^{+ve}$ and 33.3% were $CD26^{-ve}$. The B cells $CD19^{+ve}/CD10^{-ve}/CD38^{-ve}$ of Bp-ALL (pro-B ALL) patients were $CD26^{-ve}$ in all cases. However, the majority of the B cells $CD19^{+ve}/CD10^{+ve}$ (common ALL) either $CD38^{+ve}$ or $CD38^{-ve}$ was $CD26^{+ve}$. In the T-ALL patients, regardless different subtypes, the cells were $CD26^{+ve}$ but in a small number of samples ($n = 8$). In AML cases more than one half of the samples were $CD26^{+ve}$.

The analyses of the complete immunophenotypic profile of all cases of acute leukemia types are summarized in Table III. The mean percentage of cells expressing CD26 in acute leukemia types as wells as in non-leukemia patients did not show significant difference indicating that CD26 expression is not leukemia associated. Amlot *et al.* (1996) showed that the mean percentage of blood T cells from healthy volunteers that expressed CD26 were 54% [32]. In the present study, the mean percentage of cells expressing CD26 in all acute leukemias tested as well as in non-leukemia patients were lower than this value and the lowest one were AML (25%) probably because the small number of leukocytes in this samples.

The plasma DPPIV activity was evaluated for all the samples. In order to compare the normal plasma enzyme activity with the plasma enzyme activity of the acute leukemia samples, we first launch the normal interval for the plasma DPPIV activity. All the plasma samples of the normal control group showed DPPIV plasma activity within the interval of 0.2 to 0.6 U/mg of total protein with a mean value of 0.36 ± 0.09 U/mg total protein. These results were used as a normal interval and normal mean value of DPPIV activity in plasma samples.

The majority of the plasma from leukemia cases showed that 80% of patients with lymphoid leukemia, 62% of patients with myeloid leukemia and 55% of the non-leukemia patients had a DPPIV plasma activity higher than the normal interval (0.2-0.6 U/mg of total protein). The mean DPPIV plasma activity value for Bp-ALL (0.87 ± 0.29 U/mg of total protein), T-ALL (1.15 ± 0.49 U/mg total protein), AML (0.75 ± 0.29 U/mg total protein) and non-leukemia cases with hematological alterations (0.80 ± 0.36 U/mg total protein) showed a statistically significant difference with the normal control group (0.36 ± 0.09 U/mg total protein) with p values of 0.0001, 0.011, 0.0001, and 0.007 respectively for a confidence interval of 95%.

In order to verify if the DPPIV enzyme activity measured in plasma was related to CD26/DPPIV an assay of inhibition of the DPPIV activity was made with the inhibitor sitagliptin phosphate (Januvia™ Merck Sharp & Dohme) [28]. The sitagliptin phosphate inhibits the DPPIV activity in 100% in all types of acute leukemia and controls tested in this

Table II. Antigen expressions according to CD26 presence or absence in patients with Bp-ALL, T-ALL and AML at diagnosis.

	$CD26^{+ve}$ (np/nt) (%)	$CD26^{-ve}$ (np/nt) (%)
Bp-ALL (n = 37)		
CD19 + /CD10 − /CD38 −	(0/2) (0)	(2/2) (100)
CD19 + /CD10 + /CD38 −	(28/35) (80)	(7/35) (20)
CD19 + /CD10 + /HLADr/CD38 +	(27/34) (79.4)	(7/34) (20.6)
T-ALL (n = 8)		
cCD3 + /CD5 + /CD2 +	(4/5) (80)	(1/5) (20)
cCD3 + /CD4 + /CD8 −	(1/1) (100)	(0/1) (0)
cCD3 + /CD4 + /CD8 +	(2/3) (66.7)	(1/3) (33.3)
mCD3 + /TdT + /CD38 +	(4/5) (80)	(1/5) (20.0)
AML (*n* = 17)	(7/12) (58.3)	(5/12) (41.7)
Total	(41/62) (66.1)	(21/62) (33.9)

(np/nt) number of positive cases/number of cases tested.

work. As sitagliptin phosphate is a selective DPPIV inhibitor we can conclude that the DPPIV plasma activity measured is related to CD26/DPPIV. The comparison of the DPPIV activity for all types of acute leukemia and non-leukemia patients shows that, although some few patients showed plasma DPPIV activity values inside the normal interval (0.2-0.6 U/mg total protein), no differences with respect to immunophenotype were observed between the group of patients with DPPIV activity inside the normal range and the group of patients with DPPIV activity higher than the normal range (Table IV). Figure 1 shows the DPPIV activity in relation to CD26 expression for all types of leukemia tested. The analysis of the correlation between the DPPIV plasma activity and the CD26 cell expression for all types of leukemia and non-leukemia samples shows a statistically significant correlation only in the B-ALL ($p = 0.008$) and T-ALL ($p = 0.005$) acute leukemia types. B-ALL shows an inverse correlation and T-ALL shows a direct correlation (Figure 1). No correlations were found between DPPIV plasma activity and the number of leukemic blasts for all types of acute leukemia and non-leukemia samples tested.

Studies of Klobusicka and Babusikova [33,34] analyzed 30 patients with the diagnosis of T-acute lymphoblastic leukemia (T-ALL) in their works they found a strong correlation between CD26 expression and DPPIV activity however both the analysis of expression and enzyme activity were done in mononuclear cells.

Ruiz *et al*. [35] have developed a multicolor cytoenzymatic method for the simultaneous analysis of CD26 surface expression and DPPIV activity in mononuclear cells by flow cytometry and with this advanced technology they analyzed normal and

Table III. Mean Percentage of antigens positive cells with respect to acute leukemia type.

	Bp-ALL (n = 37)	T-ALL (n = 8)	AML (n = 17)	Non-leukemia Control (n = 9)
	Mean Percentage ± S.D. (np/nt) (%)			
CD26 +	48.6 ± 32.3 (78.4)	32.7 ± 39.3 (50.0)	25.3 ± 32.6 (41.2)	44.5 ± 33.7 (66.7)
CD19 +	77.2 ± 24.1 (97.3)	2.3 ± 3.4 (0.0)	11.9 ± 21.1 (17.6)	25.2 ± 26.0 (33.3)
CD10 +	78,6 ± 26.0 (94.6)	28.2 ± 39.6 (33.3)	2.76 ± 3.9 (0.0)	18.6 ± 33.4 (20)
CD2 +	13.8 ± 17.2 (15.3)	61.6 ± 42.2 (71.4)	17.7 ± 20.5 (31.3)	42.4 ± 34.9 (55.6)
CD38 +	85.2 ± 19.5 (97.3)	74.7 ± 33.2 (85.7)	72.6 ± 24.8 (100.0)	64.0 ± 27.1 (88.9)
TdT	74.1 ± 27.1 (94.6)	66.4 ± 45.5 (71.4)	5.29 ± 7.5 (5.9)	1.83 ± 3.0 (0.0)
HLADr	81.6 ± 20.9 (97.1)	4.0 ± 3.0 (0.0)	44.1 ± 30.8 (68.8)	36.1 ± 24.4 (77.8)
CD4 +	17.6 ± 18.5 (36.4)	42.7 ± 40.8 (57.1)	26.9 ± 21.7 (52.9)	27.7 ± 18.9 (62.5)
CD8 +	21.5 ± 18.6 (42.9)	38.4 ± 30.5 (71.4)	28.0 ± 27.0 (52.9)	22.1 ± 18.2 (55.6)
cCD3 +	20.0 ± 22.6 (33.3)	91.3 ± 11.1 (100)	15.8 ± 21.2 (25)	38.3 ± 32.8 (50)
mCD3 +	13.0 ± 13.4 (16.2)	37.1 ± 29.7 (71.4)	11.2 ± 14.6 (25)	44.4 ± 36.1 (55.6)
CD1a +	2.64 ± 6.0 (5.6)	28.7 ± 39.5 (42.9)	3.0 ± 5.2 (0.0)	0.5 ± 1.2 (0.0)
CD5 +	9.5 ± 14.5 (11.1)	70.7 ± 32.2 (85.7)	14.0 ± 22.3 (23.5)	39.3 ± 32.6 (55.6)
CD13 +	7.8 ± 18.1 (11.1)	32.4 ± 40.9 (42.9)	38.1 ± 27.7 (70.6)	2.3 ± 1.5 (0.0)
CD33 +	20.2 ± 21.0 (35.1)	2.0 ± 3.4 (0.0)	53.7 ± 31.4 (88.2)	4.4 ± 1.5 (0.0)
CD45 +	65.4 ± 28.5 (86.5)	73.8 ± 37.1 (83.3)	68.1 ± 33.3 (82.4)	67.1 ± 37.8 (75)
CD34 +	43.4 ± 33.2 (67.6)	0.57 ± 0.79 (0.0)	41.7 ± 34.9 (64.7)	0.8 ± 1.8 (0.0)

(np/nt) number of positive cases/number of cases tested.

Table IV. Percentage of antigen positive cells with respect to immunophenotype and DPPIV activity in the plasma.

	Bp-ALL (n = 36)		T-ALL (n = 6)		AML (n = 16)		Non-leukemia Control (n = 9)	
	[a]DPPIV$^+$ (n = 7)	[b]DPPIV$^+$ (n = 29)	[a]DPPIV$^+$ (n = 1)	[b]DPPIV$^+$ (n = 5)	[a]DPPIV$^+$ (n = 6)	[b]DPPIV$^+$ (n = 10)	[a]DPPIV$^+$ (n = 4)	[b]DPPIV$^+$ (n = 5)
	Mean Percentage ± S.D.							
CD26 +	64.79 ± 28.21	46.40 ± 31.87	0	38.86 ± 42.79	18.57 ± 23.08	29.71 ± 39.22	60.88 ± 25.56	31.38 ± 35.96
CD19 +	88.29 ± 7.18	74.17 ± 26.28	9.00	1.00 ± 1.00	4.17 ± 6.55	17.70 ± 26.03	6.50 ± 3.54	34.50 ± 27.97
CD10 +	87.43 ± 5.94	76.17 ± 28.85	0	56.00 ± 39.85	2.33 ± 3.01	2.80 ± 4.61	1.50 ± 0.71	30.00 ± 41.76
CD2 +	18.86 ± 18.95	12.75 ± 17.2	0	86.25 ± 5.68	7.33 ± 3.88	23.11 ± 25.41	36.75 ± 36.25	47.00 ± 37.30
CD38 +	83.43 ± 30.94	86.03 ± 16.59	97.00	84.25 ± 12.69	61.33 ± 26.07	77.90 ± 24.03	61.67 ± 27.54	65.40 ± 29.98
TdT	72.0 ± 20.78	74.03 ± 29.05	0	93.25 ± 4.99	6.67 ± 7.03	4.70 ± 8.43	0	2.75 ± 3.40
HLADr	91.17 ± 6.76	79.32 ± 22.74	5.00	3.75 ± 2.63	41.50 ± 33.97	49.78 ± 29.31	37.25 ± 24.81	35.20 ± 26.96
CD4 +	18.71 ± 18.95	16.80 ± 19.74	6.00	72.00 ± 25.68	22.33 ± 18.15	27.50 ± 24.20	29.33 ± 20.11	26.80 ± 20.56
CD8 +	25.0 ± 11.75	20.96 ± 20.36	24.00	50.50 ± 33.17	34.67 ± 27.44	26.70 ± 27.62	23.50 ± 22.59	21.00 ± 16.55
cCD3 +	20.29 ± 26.35	19.29 ± 22.25	82.00	97.25 ± 1.71	4.67 ± 6.02	15.33 ± 9.86	42.50 ± 44.55	36.25 ± 33.36
mCD3 +	18.14 ± 20.38	11.90 ± 11.61	90.00	30.50 ± 17.48	2.80 ± 2.17	16.00 ± 16.83	43.25 ± 39.68	45.40 ± 37.82
CD1a +	0.17 ± 0.41	3.21 ± 6.55	0	50.00 ± 41.37	0.05 ± 0.55	4.67 ± 6.60	0	0.75 ± 1.50
CD5 +	13.43 ± 15.01	8.68 ± 14.70	85.00	81.25 ± 11.21	3.17 ± 2.64	13.50 ± 16.01	31.50 ± 30.60	45.60 ± 36.21
CD13 +	5.29 ± 7.02	7.21 ± 19.19	89.00	14.75 ± 28.17	40.33 ± 27.26	35.50 ± 30.32	1.00 ± 0	3.00 ± 1.41
CD45 +	64.14 ± 28.0	64.72 ± 29.08	99.00	87.33 ± 9.71	41.00 ± 27.34	82.30 ± 28.28	50.33 ± 35.12	77.20 ± 39.26
CD34 +	38.71 ± 24.31	43.17 ± 35.09	0	1.00 ± 0.82	34.17 ± 28.66	43.80 ± 40.06	0	1.33 ± 2.31
CD33 +	29.14 ± 24.42	18.10 ± 20.43	1.00	3.25 ± 4.03	52.67 ± 36.51	54.70 ± 31.71	5.50 ± 2.12	3.67 ± 0.58
CD61 +	2.71 ± 3.60	2.17 ± 3.37	0	6.50 ± 13.00	0.50 ± 0.55	6.00 ± 10.83	3.50 ± 4.95	9.00 ± 10.23

[a] DPPIV activity in plasma is between 0.2 and 0.6 U/mg total protein; [b] DPPIV activity in plasma is higher than >0.6 U/mg total protein.
n = number of patients or controls.

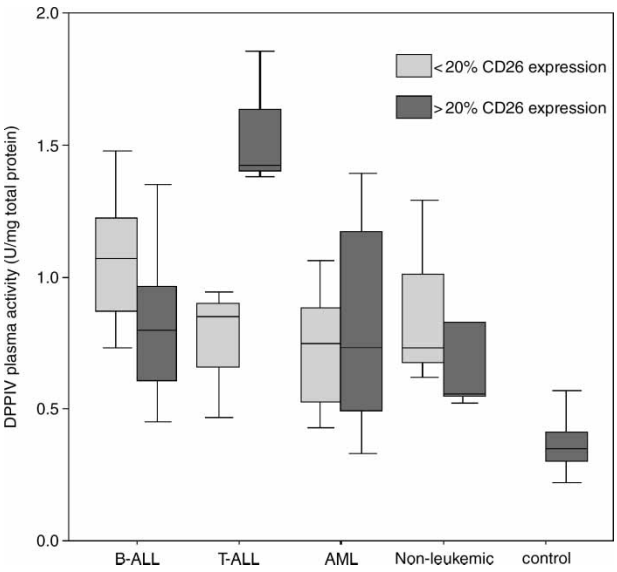

Figure 1. Mutual relation among the DPPIV plasma activity of patients of acute leukemia and the CD26 expression status in each case. The DPPIV plasma activity was plotted in relation to CD26 < 20% and >20% expression in mononuclear cells for each type of leukemia tested. Non-leukemic cases were patients with others hematological alterations and control were samples from healthy donors.

neoplastic human T-lymphocyte populations and did not find a correlation between CD26 surface expression and DPPIV enzyme activity.

Our results of correlation between CD26 expression and DPPIV activity in T-ALL are consistent with the results obtained by Klobusika *et al*. although our analysis of DPPIV activity have been performed in plasma and with other methodology.

There are divergent studies in the literature on the correlation between the CD26 expression and the DPPIV enzyme activity, in their work Ruiz *et al*. did not identified correlation between CD26 expression and DPPIV activity. The CD26 expression in T cells is related with the stage of activation and maturity of the cells and DPPIV activity may be affected by microenvironment. Contradictions between CD26 expression and DPPIV activity are not clear yet and more studies are necessary to elucidate this question.

Conclusion

The DPPIV activity in plasma of patients with acute leukemia is elevated and the inhibition assay with sitagliptin phosphate was able to inhibit in 100% this enzyme activity. As studies have been showing that the modulation of DPPIV activity could be a therapeutic target for cancer and immune disorders [27]. Further studies are required to show if the elevated DPPIV activity in plasma of acute leukemia patients could be an additional therapeutic target for leukemia therapy.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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