Leucemia linfocítica crônica. Epigallocatequina-galato aumenta apoptose e inibe VEGF – quatro estudos

**VEGF receptor phosphorylation status and apoptosis is modulated by a green tea component, epigallocatechin-3-gallate (EGCG), in B-cell chronic lymphocytic leukemia.**


**Source**

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**Abstract**

We recently reported that chronic lymphocytic leukemia (CLL) cells synthesize and release vascular endothelial growth factor (VEGF) under normoxic and hypoxic conditions. CLL B cells also express VEGF membrane receptors (VEGF-R1 and VEGF-R2), suggesting that they use VEGF as a survival factor. To assess the mechanism of apoptosis resistance related to VEGF, we determined the impact of VEGF on CLL B cells, and we studied the impact of epigallocatechin-3-gallate (EGCG), a known receptor tyrosine kinase (RTK) inhibitor, on VEGF receptor status and viability of CLL B cells. VEGF165 significantly increased apoptotic resistance of CLL B cells, and immunoblotting revealed that VEGF-R1 and VEGF-R2 are spontaneously phosphorylated on CLL B cells. EGCG significantly increased apoptosis/cell death in 8 of 10 CLL samples measured by annexin V/propidium iodide (PI) staining. The increase in annexin V/PI staining was accompanied by caspase-3 activation and poly-adenosine diphosphate ribose polymerase (PARP) cleavage at low concentrations of EGCG (3 microg/mL). Moreover, EGCG suppressed the proteins B-cell leukemia/lymphoma-2 protein (Bcl-2), X-linked inhibitor of apoptosis protein (XIAP), and myeloid cell leukemia-1 (Mcl-1) in CLL B cells. Finally, EGCG (3-25 microg/mL) suppressed VEGF-R1 and VEGF-R2 phosphorylation, albeit incompletely. Thus, these results suggest that VEGF signaling regulates survival signals in CLL cells and that interruption of this autocrine pathway results in caspase activation and subsequent leukemic cell death.

PMID:14996703
All three receptors for vascular endothelial growth factor (VEGF) are expressed on B-chronic lymphocytic leukemia (CLL) cells.


Source

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Abstract

B-chronic lymphocytic leukemia (B-CLL) cells have a long survival owing to an alteration in the normal pathways of apoptosis. CLL cells have been found to produce and secrete vascular endothelial growth factor (VEGF). In addition to its major role in angiogenesis, VEGF affects cell survival by interfering with apoptosis. The aim of the present study was to investigate the expression of the VEGF receptors VEGFR-1, VEGFR-2, and VEGFR-3 on B-CLL cells, singly and combined. B-CLL cells were isolated from peripheral blood drawn from patients with CLL. Total VEGF receptor, examined in 13 samples by flow cytometry was present in all cases with mean CD19+/VEGF+ expression of 76% (range 52-92%). Specific receptor expression, examined in 27 samples by immunocytochemical methods, was positive for VEGFR-1 in all 27 patients and for VEGFR-2 and VEGFR-3 in 26 (96%). These findings suggest that the VEGF transduction pathway may be very active in CLL cells, and both its paracrine and autocrine pathways may contribute to their enhanced survival.

Comment in


PMID:14687619
Circulating vascular endothelial growth factor (VEGF) and its soluble receptors in patients with chronic lymphocytic leukemia.

Gora-Tybor J, Blonski JZ, Robak T.

Source

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Abstract

The vascular endothelial growth factor (VEGF) transduction pathway may be very active in B-cell chronic lymphocytic leukemia (B-CLL) cells and contributes to their enhanced survival. Vascular endothelial growth factor receptor-1 (VEGFR-1) and receptor-2 (VEGFR-2), are the high-affinity VEGF receptors, which play an important role in de novo blood vessel formation and hematopoietic cell development. The aim of our study was to compare the concentration of VEGF, VEGFR-1 and VEGFR-2 in the serum of 83, never-treated B-CLL patients in different stage of disease according to Rai classification, and 20 healthy volunteers. Of all the cytokines only the serum concentration of VEGF was found to be significantly higher in the CLL group when compared to the control group (median 468.2 pg/mL and 246.9 pg/mL, respectively) (p = 0.01). In the group of CLL patients, the serum concentrations of VEGF and VEGFR-2 were significantly higher in patients in Rai stage III and IV (median 890.0 pg/mL and 4680.4 pg/mL respectively) than in patients in Rai stage 0-II (347.8 pg/mL and 2411.6 pg/mL respectively) (p<0.0001). In the entire group of CLL patients, we have found a strong, positive correlation between the serum level of VEGF and VEGFR-2 (p = 0.00001, R = 0.46). We have also found a positive correlation between the number of lymphocytes in the peripheral blood of CLL patients and the level of VEGF (p = 0.05, R = 0.24) and VEGFR2 (p = 0.02, R = 0.29). In conclusion: VEGF and VEGF R2, but not VEGF R1, may have an important influence on the course of B-CLL.

PMID:15809205
High levels of vascular endothelial growth factor receptor-2 correlate with shortened survival in chronic lymphocytic leukemia.


Clin Cancer Res. 2001 Apr;7(4):795-9

Source

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Abstract

Vascular endothelial growth factor receptor-2 (VEGFR-2), also termed KDR, is a high-affinity vascular endothelial growth factor (VEGF) receptor. VEGFR-2 plays a role in de novo blood vessel formation and hematopoietic cell development. Recently, we found that chronic lymphocytic leukemia (CLL) cells express high levels of VEGF. Therefore, we sought to investigate the role of VEGFR-2 in CLL. Using Western blot analysis, we first determined that VEGFR-2 is present in peripheral blood CLL cells. We then quantified the cellular levels of VEGFR-2 protein using a solid-phase radioimmunoanalysis in peripheral blood cells from 216 patients with CLL. As control, we used peripheral blood mononuclear cells (PBMCs) from 31 hematologically normal individuals. The median of VEGFR-2 levels detected in the control samples was assigned a value of 1.0, and VEGFR-2 protein levels were normalized to the control median value. The median level of VEGFR-2 in CLL cells was 1.57. Patients with VEGFR-2 levels higher than 1.57 had elevated lymphocyte counts, severe anemia, elevated beta(2)-microglobulin and advanced-stage disease. Elevated VEGFR-2 levels were also associated with statistically significantly shorter survival (35.4 versus 60.1 months; P < 0.01). Our data indicate that cellular VEGFR-2 levels may serve as a prognostic factor in CLL. Further studies should investigate the biological implications of these findings and the effect of the interaction between VEGF and VEGFR-2 on CLL cell proliferation.

PMID:11309324