Epigallocatechin-3-gallate Inhibits Tax-dependent Activation of Nuclear Factor Kappa B and of Matrix Metalloproteinase 9 in Human T-cell Lymphotropic Virus-1 Positive Leukemia Cells

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Abstract

Epigallocatechin-3-gallate (EGCG) is the most abundant polyphenol molecule from green tea and is known to exhibit antioxidative as well as tumor suppressing activity. In order to examine EGCG tumor invasion and suppressing activity against adult T-cell leukemia (ATL), two HTLV-1 positive leukemia cells (HuT-102 and C91-PL) were treated with non-cytotoxic concentrations of EGCG for 2 and 4 days. Proliferation was significantly inhibited by 100 μM at 4 days, with low cell lysis or cytotoxicity. HTLV-1 oncoprotein (Tax) expression in HuT-102 and C91-PL cells was inhibited by 25 μM and 125 μM respectively. The same concentrations of EGCG inhibited NF-kB nuclearization and stimulation of matrix metalloproteinase-9 (MMP-9) expression in both cell lines. These results indicate that EGCG can inhibit proliferation and reduce the invasive potential of HTLV-1-positive leukemia cells. It apparently exerted its effects by suppressing Tax expression, manifested by inhibiting the activation of NF-kB pathway and induction of MMP-9 transcription in HTLV-1 positive cells.

Keywords: Acute T-cell leukemia - human T-cell lymphotropic virus type I (HTLV-1) - Tax - NF-kB pathway
A few studies have demonstrated that arsenic trioxide (As$_2$O$_3$) potentiates the apoptotic effect of antiviral therapy and induces cell cycle arrest, partly through Tax proteasomal degradation and hence leads to NF-kB inactivation (El-Sabbab et al., 2000). The clinical use of As$_2$O$_3$ in combination with AZT/IFN showed an impressive 100% response rate without relapse (Khour et al., 2009). However, the safety evaluation of this combination showed some haematological and non-haematological toxicity such as lung infiltration of ATL cells, confusion, arrhythmia, hepatic cytolysis. These results suggest that the triumvirate of AZT, IFN-γ and As$_2$O$_3$ is a promising approach but warrants further investigation to overcome its toxicity effect. Therefore, targeting viral replication and Tax oncoprotein has a strong potential for treatment of ATL. It is expected that research into discovering a treatment which combines the benefits of the aforementioned compounds and the lack of toxicity thereof could have a powerful impact in ATL therapy.

Green tea extract has shown good potential in the treatment of cancer. Catechins, a special group of polyphenols, are the active component of green tea with antioxidative properties (Singh BN et al., 2011). The most important and abundant catechin found in green tea is epigallocatechin-3-gallate (EGCG). EGCG has a chemopreventive, anti-mutagenic, and anti-inflammatory activities mainly attributed to its pro-apoptotic effects on leukemic cells (Suganuma et al., 2011). Previous work has indicated that EGCG inhibits the invasiveness of cells by negating the activity of MMPs and inhibits MMP-2 and MMP-9 through direct binding and the formation of reversible EGCG-MMP complexes (Tanimura et al., 2005). Furthermore, EGCG was found to induce apoptosis and inhibit cell cycle and progression by inhibiting NF-kB (Singh et al., 2011). To the best of our knowledge, there are no reports on the effect of EGCG on Tax thus far.

In light of what was mentioned above, we tested various concentrations of EGCG on two HTLV-1-positive cell lines and we focused on the effect of EGCG on MMP activity, NF-kB DNA binding and Tax. The ultimate aim was to investigate whether EGCG can, by itself or in combination with other agents, be effectively employed in ATL therapy. Herein, we show that EGCG exhibits properties that warrant its consideration in ATL therapy.

Materials and Methods

Cell lines and EGCG

Two HTLV-1 positive ATL cell lines were used, namely HuT-102 and C91-PL (provided by Dr. A. Gessain, Institut Pasteur Paris, France). The cells were grown in RPMI 1640 complete growth media with 25 mM of Hepes, supplemented with 10% Fetal Bovine Serum, 100 µg/ml of Streptomycin and 100 U/ml of Penicillin. Cells were routinely grown at 37°C in a 5% CO$_2$-humidified incubator. EGCG was obtained in a powder form from Sigma (St. Louis, MO). Fifty milligrams of EGCG were dissolved in 5 ml of RPMI 1640 media. The EGCG solutions were distributed into aliquots and stored at -20°C. At the time of conducting the experiment, one aliquot was thawed, diluted, kept on ice and used immediately in the designed experiment.

Cell growth and cytotoxicity

Cytotoxicity of EGCG was assayed using CytoTox 96 Non-radioactive Cytotoxicity Assay (Promega, Corp., Madison, WI), a method which measures the amount of lactate dehydrogenase (LDH) released from dead cells. Proliferation was measured using Cell Titer96TM Nonradioactive Cell Proliferation kit (Promega Corp., Madison, WI), which measures the ability of metabolically active cells to convert tetrazolium salt into a colored formazan product. Experiments were carried out according to the instructions of the manufacturer.

Nuclear extraction

The HTLV-1 positive cell lines were grown in the presence or absence of the test compound and harvested at the end of the experiment. For nuclear extraction, cells were centrifuged and washed twice with 1 ml of ice-cold phosphate buffered saline (PBS) and frozen at -80°C. Cells were re-suspended in 70 µl of hypotonic ice-cold buffer A (10 mM HEPES, 10 mM KCl, 1.5 mM MgCl$_2$, 1 mM DTT) and the cell suspension was pelleted for 10 mins at 4°C using a microcentrifuge at 3,500 rpm. The supernatant was discarded and the nuclei were lysed in 15 µl of buffer B [20 mM HEPES, 400 mM NaCl, 1.5 mM MgCl$_2$, 0.2 mM methylenediaminetetraacetic acid (EDTA), 1 mM DTT, 0.5 mM phenylmethylsulfonyl-fluoride (PMSF) and 25% glycerol]. Extraction was completed by gentle mixing for 30 mins at 4°C. The nuclear debris was removed by pelleting the extracts in a microcentrifuge at 14,000 rpm for 20 mins at 4°C. The supernatant was discarded and the pellet was diluted in buffer D (20 mM HEPES, 50 mM KCl, 20% glycerol, 0.2 mM EDTA, 1 mM DTT and 0.5 mM PMSF) and stored at -80°C. Protein concentrations were determined using the Bio-Rad DC Protein Assay Kit (BioRad Laboratories, Hercules, CA), with inclusion of bovine serum albumin as a standard.

ELISA and EMSA for NF-kB

Nuclear extracts obtained from cells treated with various non-cytotoxic concentrations of the test compound were used under different experimental conditions after dilution in appropriate amounts of buffer to reach the desired concentration. For the Enzyme Linked Immunosorbant Assay (ELISA), the 96-well plate, supplied with the kit (Roche, Mannheim, Germany), was coated with anti-p65 antibody (Santa Cruz Biotechnology Inc., Santa Cruz, CA), and the procedure was followed according to the manufacturer’s instructions. For EMSA, NF-kB consensus oligonucleotides and mutant sequences (see Table 1) were end-labeled with $\gamma$-32P ATP, using T4-polynucleotide kinase, and the assay was performed as described previously (Harakeh et al., 2006).

RT-PCR mRNA expression of MMP-9

Both cells treated or untreated for 96 h with the test compound were collected and stored at -70°C. Total RNA was extracted from the cells using NucleoSpin RNA II kit (Macherey, Nagel) and quality control was assessed using gel electrophoresis (data not shown). After testing different
RNA concentrations, two micrograms of mRNA were reverse transcribed into first strand cDNA using One Step RT-PCR kit (Reddy Mix Version) (Abgene, Promega). Reaction was conducted in 50μl volume using specific oligonucleotide primers designed to detect the MMP-2 and MMP-9 and ribosomal phosphoprotein according to conditions shown in table 1. The 50μl mixture contained in addition to the RNA, 25μl of 2xReddy Mix RT-PCR Master Mix, 1μl of 10 μM sense primer, 1μl of 10μM anti-sense primer, 1μl of the reverse transcriptase blend (50units/μl), and RNase-DNase-free water that would adjust the volume to 50μl. Ribosomal phosphoprotein was used to ensure equal loading.

Western blotting for protein expression of MMP-9 and Tax

The HTLV-1-positive cells were lysed in a buffer containing 50mM Tris–HCl, pH 7.5, 150mM NaCl, 1% Nonidet P40, 0.5% sodium deoxycholate, 4% protease inhibitors, and 1% phosphatase inhibitors. Cells were transferred to boiling water for 5 min. After cooling, cells were centrifuged at 14,000 rpm for 10 min. The supernatants were collected and placed on ice. Protein concentrations were determined using the DC BioRad protein assay kit (BioRad Laboratories, Hercules, CA), including bovine serum albumin as a standard. A total of 30 μg of cellular protein was loaded onto 10% SDS-polyacrylamide gels. The separated protein bands were then transferred electrically to PVDF membranes (NEN Life Sciences Products, Boston,MA). The Primary antibodies specific to MMP-9, Tax, and GAPDH were obtained from SantaCruz Biotechnology Inc. (Santa Cruz, CA) and used for immunoblotting. Subsequently, membranes were probed with horseradish peroxidase-conjugated secondary antibody (Bio-Rad, Hercules, CA) and used for immunoblotting. Subsequently, membranes were probed with horseradish peroxidase-conjugated secondary antibody (Bio-Rad, Hercules, CA). The detection procedure of the protein bands was performed using an enhanced chemiluminescence system, and according to the manufacturer’s instructions. Banded proteins were developed on X-ray film using an Xomat machine (Amersham, Pharmacia, Biotech).

Zymography for activity of MMP-9

Cells were treated with various concentrations of EGCG for three days and then starved, by removing the FBS from the growth medium, for 24 hours and treating the cells with various concentrations of the test compound. Cells were centrifuged and the supernatant was collected and concentrated by 10-fold. Appropriate amounts of the supernatant were loaded on 10% acrylamide gels with 10% gelatin and run at 90V. The gels were washed twice and concentrated by 10-fold. Appropriate amounts of the protein band were excised from the gel and extracted with sample buffer and were incubated in substrate buffer for 18 hours at 37°C [substrate buffer (50 mM Tris-Cl, 5 mM CaCl2, 150 mM NaCl) and Triton X-100] and then removed from the substrate buffer, stained by Coomassie Blue for 4 hours at 37°C, and washed with double distilled water to remove the extra stain. The bands resulting from the digestion were visualized using white light and photographed for documentation.

Results

Antiproliferative effects of noncytotoxic concentrations of EGCGs

Concentrations of EGCG ranging from 0 to 400 μM were selected to evaluate EGCG cytotoxicity and antiproliferative effect on HuT-102 and C91-PL cells lines. The tested concentrations did not inhibit proliferation and were non-cytotoxic on both cell lines after 24 h of treatment (Data not shown). However, antiproliferative effects were seen at 48 and 96 h of treatment and a pronounced antiproliferative effect of EGCG was consistently noted at 96 h as compared to 48h (Figure 1). The used concentrations were non-cytotoxic in primary cultures of normal T-lymphocytes isolated from humans (Data not shown).

Cytotoxicity was observed at an EGCG concentration of 400 μM and after an incubation period of 48h as

![Figure 1. Cytotoxicity and Antiproliferative Effect of EGCG. The effect of EGCG on cytotoxicity (a, c) and proliferation (b, d) of HuT-102 (a,b) and C91-PL (c,d). HTLV-1 positive cell lines are presented. Each value is the mean±SD deduced of three separate experiments done in triplicate.](https://example.com/figure1.png)

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Table 1. Synthetic Oligonucleotides and Experimental Conditions used for RT-PCR and EMSA Analysis.
opposed to the cytotoxic effect obtained by a concentration of 300 µM at 96h of exposure to HuT-102 cells (Figure 1a). The C91-PL cells were more susceptible to EGCG treatment (Figure 1c). An inhibition of proliferation equivalent to 41.8% was achieved in HuT-102 cells when grown in the presence of 200 µM of EGCG (Figure 1b). The incubation with different EGCG concentrations for a period of 24h did not produce any antiproliferative effects in C91-PL cells at all the tested concentrations (Figure 1d). A marked antiproliferative effect of EGCG on HuT-102 cells was observed at a concentration of 100 µM, resulting in 35% inhibition. However, a lower concentration of 25 µM of EGCG was needed to inhibit the C91-PL proliferation by 46% after an incubation period of 96h (Figure 1d, 1b).

Therefore, in all subsequent experiments only the non-cytotoxic concentrations of EGCG (25-75 µM) were applied to C91-PL and concentrations of 125-325 µM were used for HuT-102 cells after extending the incubation period to 96h.

**Effect of EGCG on Tax expression**

EGCG induced a dose-dependent decrease in the protein levels of Tax in both HTLV-I-positive cell lines (Figure 2). In the HuT-102 cell line, there was a considerable inhibition of Tax levels at an EGCG concentration of 225 µM. However, in the case of C91-PL, an inhibition of Tax was observed at 25 µM of EGCG. Tax protein was more evidently expressed in HuT-102 than C91-PL cell line with a 5.6 fold increase in band intensity (Data not shown).

**Effect of EGCG on NF-κB activity**

A supershift assay was performed on both HuT-102 and C91-PL and revealed the presence of the p65/p50 heterodimer in the nucleus of both cell lines (data not shown).

After EGCG treatment, there was a decrease in the binding of the p65/p50 heterodimer to its DNA sequence in both HuT-102 and C91-PL (Figure 3A, 3B). In the case of HuT-102, the inhibition was greater than that in C91-PL. The highest inhibition was observed in HuT-102, reaching up to 66% at a concentration of 325 µM EGCG whereas the maximum inhibition in C91-PL was noted at a concentration of 75 µM EGCG, reaching only to 30%. The specificity of p65 binding to NF-κB consensus probe was determined using cold and mutant probes (data not shown).

The results of ELISA in quantitative assessment of p65 in the nucleus show that there was a reduction in the levels of p65, indicating a decrease in the binding of the p65 subunit from the cytoplasm to the nucleus as a result of treatment with EGCG. The inhibition was greater in C91-PL and to a lesser extent in HuT-102, reaching around 67% and 50%, respectively. The reductions were obtained at the highest applied concentrations of EGCG in both cell lines (Figure 3C, 3D).

**Effect of EGCG on MMP-9 expression and activity**

To evaluate the effect of EGCG on the transcriptional level of MMP-9, RT-PCR was employed to quantify its mRNA level. The cells were treated with EGCG for 96 h and mRNA was isolated, quantified and amplified using RT-PCR. PCR results were run on agarose gels. EGCG reduced the mRNA levels of MMP-9 in both cell lines and the exhibited inhibitory effect was dose-dependent,
with a more apparent effect observed on C91-PL cell line. The effect of EGCG on mRNA level of MMP-9 in HuT-102 and C91-PL was determined at 225 μM and 50 μM, respectively (Figure 4A).

To further evaluate the effect of the test compound on invasion potential of malignant cells, the translational level of MMP-9 was measured by Western Blotting. Cells were treated for 96 h with EGCG and the protein level of MMP-9 was determined using specific antibodies (see materials and methods). A dose-dependent decrease in the levels of MMP-9 in the HTLV-positive cell lines was noticed, culminating in complete inhibition of this protein at the highest dose of EGCG (Figure 4B). The translational levels of MMP-9 (Figure 4B) were more susceptible to EGCG than the transcriptional level of its mRNA (Figure 4A), with a more distinct effect of EGCG in HuT-102 and C91-PL cells at 125 μM and 25 μM, respectively.

To explore the effect of EGCG treatment on cellular invasion potential, zymography was used. EGCG induced a down-regulation of MMP-9 activity in both cell lines in a dose-dependent manner (Figure 4C). The quantification of protein bands which were obtained from cytoplasmic (Figure 4B) and supernatant extracts (Figure 4C) revealed that the MMP-9 activity was more susceptible to EGCG treatment than the translated protein level, particularly in HuT-102 cell line (data not shown).

**Discussion**

It has been reported that EGCG induces apoptosis and cell cycle arrest in vitro in both HTLV-1 infected and non-infected malignant T-lymphocyte cell lines (Li et al., 2000; Harakeh et al.; 2008). In this work, we have investigated the effects of EGCG on Tax expression, NF-kB activation and the MMP-9 target gene implicated in invasion of ATL HTLV-1 positive cells.

The concentrations of EGCG (< 400 μM) used in this work for inhibiting proliferation were similarly reported by others (Li et al., 2000). No antiproliferative effect was noted at 24h of incubation in both cell lines. We assumed that the cells needed to undergo few replication cycles in the presence of the test compound before an effect is observed. As a result, the antiproliferative effect of EGCG was seen at concentrations of 100 μM at contact times of 48h and 96 h. This is in agreement with other reported results, using human and mouse leukemic cells, in which a concentration of 100 μM of EGCG was able to inhibit the DNA synthesis (Otsuka et al., 1998).

The results reported herein show, for the first time, that EGCG had an effect on Tax oncoprotein expression in both cell lines. A dose-dependent decline in Tax protein levels was noted in HuT-102 and C91-PL cells. In a different published work by Li et al., it was shown that a level of 3-27 μg/ml of either green tea polyphenols or EGCG can induce an inhibitory activity on HTLV-I pX mRNA (Li et al., 2000). Tax is a 40 kDa viral oncoprotein encoded by the pX region of the HTLV-I genome. It is an essential activator of viral gene expression via the long terminal repeats (LTR), specifically through the 21-bp repeat elements located within the LTR and it is referred as Tax-responsive element 1 (TRE1) (Lairmore et al., 2012). In addition, Tax regulates the expression of a large variety of cellular genes through different signaling pathways such as c-AMP responsive elements binding (CREB), nuclear factor kappa B (NF-kB), serum response factor (SRF), to some extent through activator protein (AP)-1, NFAT, janus kinase/signal transducer, activator of transcription (JAK/STAT) and transforming growth factor (TGF)-β pathways. As a consequence, Tax induces cell immortalization in vitro as well as tumor formation in transgenic mice by deregulating cell cycle and inhibiting apoptosis (Rauch and Ratner, 2011). This effect is mainly due to the activation of antiapoptotic genes such as BCL-3, BCL-XL, c-FLIP and cIAP-2 through the stimulation of NF-kB pathway (Nicot C et al., 2000; Okamoto et al., 2006; Zane et al., 2010; Wang et al., 2013). It should be noted that unlike the transiently acting external signals, Tax renders the NF-kB factors constitutively active in HTLV-1 infected cells (Tabakin-Fix et al., 2006). This fact requires an intensive effort to focus on developing novel approaches for blocking the persistent NF-kB activity as a therapeutic strategy for such clinical disorders (Marçais et al., 2013).

Analysis of EGCG effects on downstream signaling of Tax indicated that EGCG mediates its activity through the NF-kB pathway in a dose-dependent manner. The NF-kB family consists of five transcription factors, p50 (NF-kB1), p52 (NF-kB2), p65 (RelA), RelB and c-Rel, acting in various combinations of homo- and heterodimers that display distinct specificities (Oeckinghaus et al., 2011). The most prominent dimers involved in NF-kB dependent transcriptional gene activation include p65 subunit (p65:p65 and p65:p50). In the non-activated state, NF-kB factors are trapped in the cytoplasm by the action of inhibitory proteins called IκBs.

It has been reported previously that pretreatment with EGCG prior to UVB irradiation inhibited the UVB-induced NF-kB activation, phosphorylation, and degradation of IκBα in a dose- and time-dependent manner (Afaq et al., 2003). Furthermore, the authors demonstrated that EGCG interfered with the translocation of the p65 subunit to the nucleus which is in agreement with our findings. This is corroborated with previously published data, showing the inhibitory effect of EGCG on the migration of the p65 subunit mediated by the Epstein-Barr (EB) virus latent membrane protein (LMP)-1. In addition, the authors reported an increase of NF-kB activity which was attributed to a rise in IκKα expression (Yan et al., 2004). Two models have been proposed for EGCG’s activity on NF-kB. One model attributed the EGCG’s down-regulation of NF-kB to its inhibition of reactive oxygen species. The other model proposed that EGCG activated the caspasas, causing a down-regulation of NF-kB (Ahmad et al., 2000). Jeong and co-workers suggested that the mechanism of NF-kB inhibition by EGCG could occur by up-regulating of p53 at the transcriptional level (Jeong et al., 2004). The down-regulation of NF-kB by EGCG may explain the mechanism by which the latter induces cell cycle deregulation and apoptosis. Inhibitors of NF-kB were found to block ATL cell proliferation and survival in vitro (Mori et al., 2002; Ohsugi et al., 2005; Uota et al., 2012).
In case of inhibition of MMP-9 by EGCG at transcriptional level, it was reported that the test compound produced its effect by inactivation of FAK/ERK/NF-κB signaling pathway using human breast cancer cell line MDA-MB-231 (Sen et al., 2010) and by inhibiting the MAPK/AP-1 signaling in human gastric cancer AGS cells (Kim et al., 2006). It has also been reported that the oxidative stress in a human epithelial lens cell line (Yao et al., 2009) and in lung carcinoma 95-D cells (Yang et al., 2005) affected the MMP-9 transcription by inhibiting the activation and translocation of NF-κB. Accordingly, it is reasonable to state that EGCG reduced MMP-9 transcription in HTLV-1-positive cell lines by inhibiting the NF-κB nuclear translocation.

Translational control of MMP-9 expression started around ten years ago when Jang and Muschel reported in 2002 a difference in the translational efficiency regulation, resulting in a change in MMP-9 secretion in murine prostate cancer cells (Jiang and Muschel, 2002). However, it was published earlier that a correlation exists between the reductions in eukaryotic translation initiation factor-4E (eIF4E) and decreasing levels in MMP-9 (Graft et al., 1995). The eIF4E is a cap-binding protein which recruits ribosomes to the 5’ end of mRNA. Phosphorylation of eIF4E by MAPK/Mnk signaling enhances its activity, while its sequestration by eIF4E-binding proteins (4E-BPs) inhibits translation (Pyronnet et al., 1999; Martineau et al., 2013). The most abundant 4E-BP1 is inactivated by hyperphosphorylation or down regulation via the P13K/mTOR signaling pathway (Azar et al., 2008). It is worth noting that Tax activates P13K/mTOR in T-lymphocytic cells and plays a crucial role in the growth of HTLV-1 infected cells (Yoshita et al., 2000). Therefore, many studies demonstrated that the activation of eIF4E or inactivation of 4E-BP1 facilitated cell proliferation and their invasive ability to various cancer cells (Azar et al., 2009; 2010). Reports on the effect of EGCG on P13K/mTOR/4E-BP1 signaling and inhibition of protein translation described the inhibition of P13K/mTOR which was achieved at concentrations of EGCG ranging from 320-380 nM EGCG (Syed et al., 2007; Van Aller et al., 2011). These reported concentrations seem to be much lower than those reported in this work. Therefore, the inhibition of MMP-9 at translational level by EGCG may be explained by its inhibition of P13K/mTOR/4E-BP1 pathway independently of the test compound on NF-κB pathway.

In conclusion, we have showed for the first time that EGCG inhibited Tax oncoprotein expression and NF-κB signaling pathway in HTLV-1-positive leukemia cells (HuT-102 and C91-PL). We have also demonstrated that EGCG down-regulated, separately, the activity of MMP-9 and its expression on both transcriptional and translational levels. Altogether, this supports the chemopreventive, rather than therapeutic, efficacy of EGCG on ATL progression and provides rational for its crucial role as a polyvalent signal transduction inhibitor.

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References


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