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Epigallocatechin-3-gallate inhibits paclitaxel-induced apoptosis through the alteration of microRNA expression in human dermal papilla cells

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Abstract

Background: Paclitaxel well known as anti-cancer drug has been shown to cause alopecia in chemotherapy. The paclitaxel chemotherapy-mediated alopecia is induced by apoptotic damage in human dermal papilla (HDP) cells. Epigallocatechin-3-gallate (EGCG) inhibits apoptosis against anti-cancer drug such as cisplatin. EGCG, one of the green tea extract ingredients, has been reported to enhance cell viability and to inhibit apoptosis. However, it is unclear that EGCG enhances cell viability and inhibits apoptosis against paclitaxel-induced apoptotic damage in HDP cells.

Methods: We show cell viability, cell cycle, and microRNA (miRNA) expression in EGCG-mediated rescue cell to paclitaxel-mediated cell death and growth arrest.

Results: EGCG promotes cell survival and cell death inhibitory effects and alteration of miRNA expression in paclitaxel-exposed HDP cells were investigated. Firstly, paclitaxel increases apoptosis and EGCG promotes cell survival and represses paclitaxel-induced apoptosis in a dose-dependent manner. Fluorescence-activated cell sorting (FACS) analysis showed that EGCG protects apoptosis in paclitaxel-exposed HDP cells. miRNA microarray analysis was performed and 48 miRNAs changed by EGCG in paclitaxel-exposed HDP cells were identified. In gene ontology analysis in silico, miRNAs regulate apoptosis and cell proliferation-regulated genes, such as *BCL2L1*, *BCL2L2*, *BBC3*, and *MDM2*. In Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis, miRNAs are related to mitogen-activated protein kinase (MAPK) signaling pathway and Wnt signaling pathway, which regulate apoptosis and cell proliferation.

Conclusions: EGCG inhibits apoptosis through regulating miRNA expression related to apoptosis and cell proliferation in paclitaxel-treated HDP cells.

Keywords: Epigallocatechin-3-gallate, Paclitaxel, Human dermal papilla cell, MicroRNA

Background

Paclitaxel, taxane-based anticancer drugs, purified in bark of *Taxus brevifolia* regulates microtubule dynamics by binding with β-tubulin (Manfredi and Horwitz 1984; Amos and Löwe 1999). Paclitaxel-mediated regulation repressed mitotic activity and then induces apoptosis. Thus, it is generally used in therapy of metastatic breast cancer, ovarian cancer, and non-small cell lung cancer (Khanna et al. 2015; Chen et al. 2011; Jordan and Wilson 2004).

In anticancer chemotherapy, the risk of potential side effects is one of the important features (Macdonald et al. 2015; Balagula et al. 2011). In the case of paclitaxel, a known side effects include leukopenia, thrombocytopenia, anemia, muscle pain, and hair loss symptoms. Especially, hair loss is the major side effects of paclitaxel (Ozcelik et al. 2010; Shapiro and Recht 2001). Paclitaxel-mediated hair loss is resulted by apoptotic damage of dermal papilla

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cells (Chen et al. 2011; McElwee et al. 2003; Yang and Cotsarelis 2010). However, it has not been identified the detailed mechanism of paclitaxel-mediated apoptotic damage of dermal papilla cells.

Hair is grown by a repetitive cycle consisted of anagen, catagen and telogen, which is regulated by HDP cells in normal and abnormal condition, such as hair loss (Inui et al. 2003; Stenn and Paus 2001). Since the HDP cells can significantly affect the hair growth, HDP cell-regulating factor is implicated in therapy of hair loss (Kwon et al. 2007; Aljuffali et al. 2015).

Recently, miRNA is studied as a factor affecting the function of the dermal papilla cells. miRNA is a non-coding small nucleotide consisted of 18–24 nucleotides and interfere translation of target genes by binding to a 3′-untranslated region (UTR) of the mRNA in the gene expression process (Bartel 2004; Bartel 2009; Carrington and Ambros 2003). miRNA is known to play a role in apoptosis, cell proliferation, and differentiation and recently has been reported that miR-31 is highly expressed in hair growth phase, which regulated the expression of Krt16, Krt17, Dlx3, and Fgf10. In addition, miR-24 is implicated in hair follicle formation through regulating known as stemness regulator of human keratinocytes role (Wan et al. 2011; Mardaryev et al. 2010; Amelio et al. 2013).

EGCG, a major compound of green tea that contained polyphenols, is effective in anti-cancer and antioxidant (Hsu 2005; Wang and Bachrach 2002; Katiyar and Elmets 2001). In addition, EGCG induced cell growth and is prevented against UV-mediated cell death in keratinocytes and HDP cells, which regulate hair growth (Kwon et al. 2007; Yang and Landau 2000; Katiyar et al. 1995; Chung et al. 2003).

In our study, we show protection activity of EGCG to paclitaxel-induced HDP cell death. Moreover, we demonstrate a cellular signaling mechanism of EGCG-mediated paclitaxel protection mechanism through analyzing alteration miRNA expression profile.

Methods

Cell culture and materials

HDP cells were maintained using Dulbecco's modified Eagle's medium (DMEM; Hyclone, Logan, UT, USA) with 1% penicillin/streptomycin (10,000 units/mL penicillin G sodium, 10,000 μg/mL streptomycin; Gibco-BRL/Invitrogen Life Technologies, Gaithersburg, MD, USA) and 10% fetal bovine serum (FBS; Hyclone) and incubated at 5% CO_2 at 37 °C. Paclitaxel was purchased from Sigma-Aldrich (St. Louis, MO, USA).

Cell viability assay

HDP cells were seeded in 96-well plates at 2×10^3 cells/well and then incubated for 24 h. After 24 h, EGCG and paclitaxel was treated with indicated concentrations for 24 h. Water-soluble tetrazolium-1 (WST-1) solution was added and incubated for 20 min. Optical density of each well was measured at 450 nm using a iMark™ microplate reader (Bio-Rad, Hercules, CA, USA). And the value was calibrated by measuring a reference absorbance at 650 nm.

Cell cycle assay

HDP cells were incubated with EGCG and paclitaxel for 24 h. Cells were harvested and washed with phosphate-buffered saline (PBS; sodium chloride 137 mM, phosphate buffer 10 mM, potassium chloride 2.7 mM, all from BioPure (Canada). After washing, cells were fixed by 70% ethanol and then stained with propidium iodide (PI) staining buffer (PI 50 μg/mL, RNase 0.1 mg/mL, 0.05% Triton X-100). Fluorescence intensity was measured by FACS Calibur (BD Biosciences, San Jose, CA, USA). And Sub-G1, G0/G1, S, and G2/M were measured by Cell Quest software (BD Biosciences).

miRNA microarray

To analyze miRNA expression profile, HDP cells were seeded and treated with EGCG and paclitaxel. After 24 h, total RNA was extracted using TRIzol reagent (Sigma-Aldrich) according to the manufacturer's instructions. Total RNA was stained with Cy3 using Agilent miRNA Labeling kit (Agilent Technologies, Santa Clara, CA, USA). Labeled RNAs were hybridized using a SurePrint G3 Human v16 miRNA 8x60K microarray (Agilent Technologies) at 65 °C for 20 h. The miRNA expression profile was analyzed using Feature Extraction version 10.7 software (Agilent Technologies) and GeneSpring GX software, version 11.5 (Agilent Technologies).

miRNA target and ontology analysis

Target genes were predicted using seed sequence-based miRNA target prediction database, TargetScan (Target scan human 2017) and miRbase (miRbase 2017). Additionally, to categorize hair follicle development, apoptosis, and cell proliferation, gene ontology of predicted target genes of miRNA was analyzed by DAVID Bioinformatics Resources 6.7 (National Institute of Allergy and Infectious Diseases 2017).

Results

Protective effects of EGCG to paclitaxel-mediated growth arrest in HDP cells

To demonstrate protection effects of EGCG in paclitaxel-mediated growth arrest, we co-treated it with paclitaxel and EGCG. As shown in Fig. 1, 5 μM EGCG decreased 1 μM paclitaxel-induced growth arrest (62%) to 84%. Furthermore, in cell cycle analysis, 1 μM paclitaxel induced cell death fraction (sub-G1) in the same

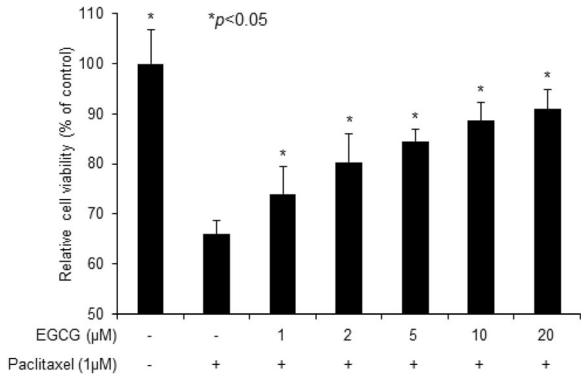

Fig. 1 EGCG protects HDP cells against paclitaxel-induced apoptosis. HDP cells were seeded into 96-well plates and pre-treated with various concentrations of EGCG (0, 1, 2, 5, 10, and 20 μM) for 4 h and post-treated with paclitaxel (1000 nM) for 24 h. Cell viability was measured using the WST-1 assay. Values are presented as the mean ± standard error of the mean of the percentage of control optical density of experiments performed in triplicate

condition. However, co-treatment with 10 μM EGCG reduced paclitaxel-mediated cell death in HDP cells (Fig. 2).

EGCG-mediated alteration of miRNA profile in paclitaxel-exposed HDP cells

We showed EGCG-mediated alteration of miRNA profile in paclitaxel-exposed HDP cells. As shown in Fig. 3, EGCG upregulated 20 miRNAs and downregulated 28 miRNAs in paclitaxel-exposed HDP cells. Among 48 miRNAs, miR-3663-3p, miR-1181, miR-3613-3p, miR-1281, and miR-1539 had increased by 293.52-fold, 241.98-fold, 188.91-fold, 177.18-fold, and 169.23-fold, respectively. Additionally, miR-221-5p, miR-374b, miR-590-5p, miR-4306, and miR-500a-5p had decreased by 132.32-fold, 124.96-fold, 122.52-fold, 116.09-fold, and 105.14-fold, respectively (Table 1).

Bioinformatic analysis of EGCG-regulated miRNAs in paclitaxel-exposed HDP cells

To analyze relation between growth arrest and cell death and EGCG-regulated miRNAs, we predicted target genes of EGCG-regulated miRNAs using TargetScan (Target scan human 2017) and miRbase (miRbase 2017). And

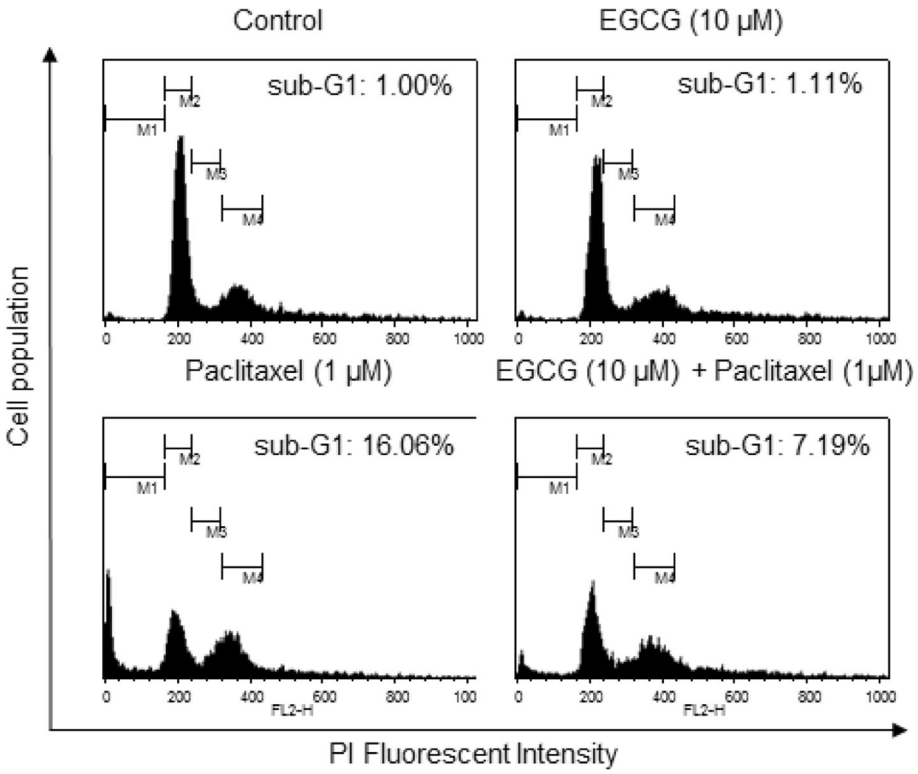

Fig. 2 Paclitaxel-induced sub-G1 arrest and cell death were inhibited by EGCG in HDP cells. Flow cytometric analysis was performed to determine the cell cycle distribution of the control HDP cells, HDP cells treated with 1000 nM paclitaxel only, HDP cells treated with 10 μM EGCG only, and HDP cells pre-treated with 10 μM EGCG followed by treatment with 1000 nM paclitaxel. The Sub-G1, G1, S, and G2/M phases were separated using gates M1, M2, M3, and M4, respectively

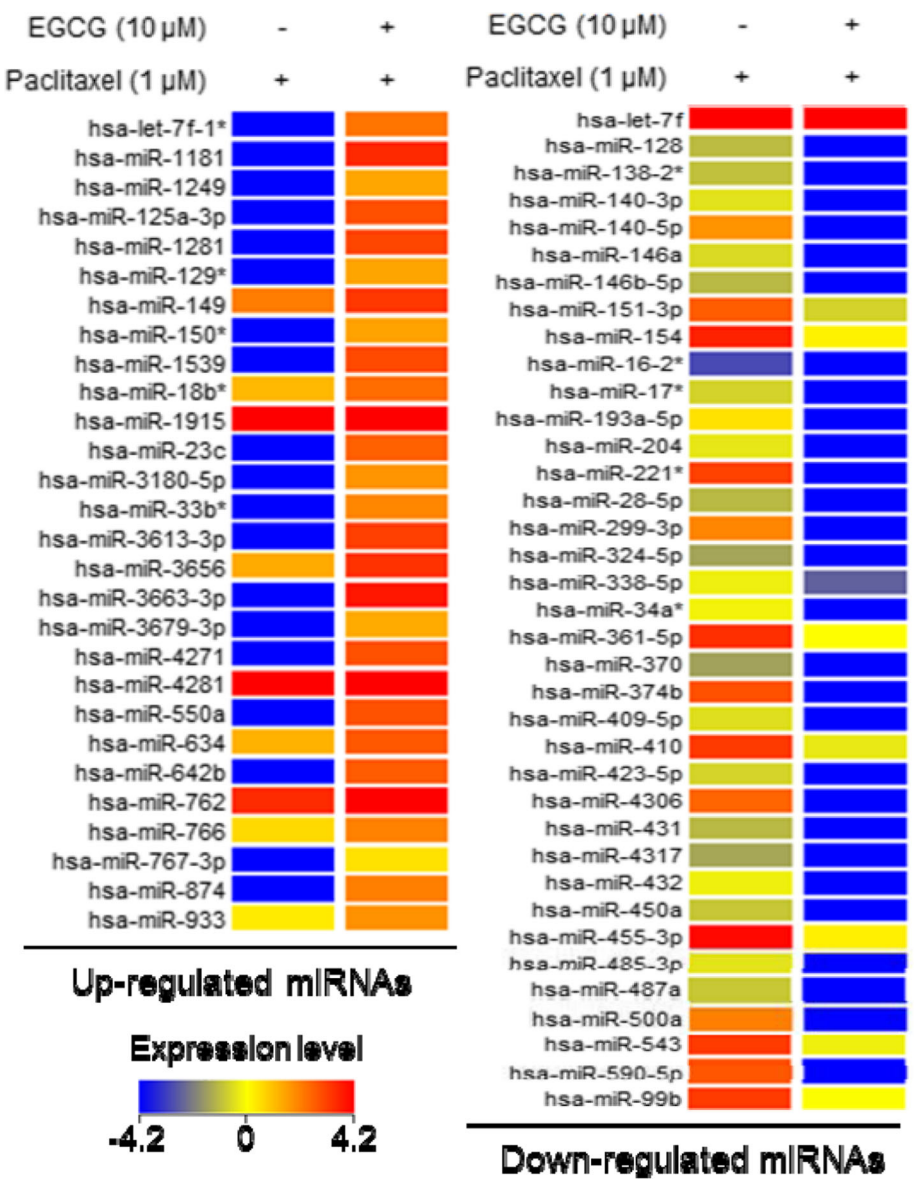

Fig. 3 EGCG alters miRNA expression profiles in paclitaxel-treated HDP cells. Heat map analysis of miRNAs upregulated and downregulated with a ≥ 2-fold change in expression in paclitaxel-treated HDP cells. HDP cells were seeded in 60-mm culture dishes and pre-incubated with 10 μM EGCG for 4 h. Following pre-treatment, the HDP cells were treated with 10 μM EGCG and 1000 nM paclitaxel and incubated for 24 h. miRNA expression was determined using the SurePrint G3 Human v16 miRNA 8x60K Microarray Kit. The color bars displaying fluorescence intensity correspond to each miRNA expression. Expression levels are indicated in the legend bar

then, in Additional file 1: Table S1 and Table S2, we categorized functions of target genes using their functions, apoptosis, cell proliferation, and hair follicle development, using DAVID (National Institute of Allergy and Infectious Diseases 2017). Additionally, to demonstrate relation between target genes of EGCG-regulated miRNAs and identified signal pathways, we analyzed signal pathway using KEGG pathway database. As shown in Additional file 1: Table S3 and Table S4, at in silico analysis, EGCG-upregulated miRNAs regulated various KEGG pathways, such as MAPK signaling pathway, pathways in cancer, neurotrophin signaling pathway, long-term depression, pancreatic cancer, chronic myeloid leukemia, colorectal cancer, ECM-receptor interaction, vibrio cholera infection, glycerolipid metabolism, lysine degradation, cell adhesion molecules (CAMs), glioma, melanoma, endocytosis, focal adhesion, ubiquitin-mediated proteolysis, ErbB signaling pathway, tight junction, Jak-STAT signaling pathway, renal cell carcinoma, adherens junction, Fc gamma R-mediated phagocytosis, epithelial cell signaling in *Helicobacter pylori* infection, p53 signaling pathway, long-term potentiation,

Table 1 miRNAs showing > 3-fold expression change following treatment with EGCG in paclitaxel-exposed HDP cells

miRNA	Change relative to controls	Direction of regulation	chr.	miRNA	Change relative to controls	Direction of regulation	chr.
hsa-miR-3663-3p	293.53	Up	chr10	hsa-miR-500a-5p	105.14	Down	chrX
hsa-miR-1181	241.98	Up	chr19	hsa-miR-299-3p	102.72	Down	chr14
hsa-miR-3613-3p	188.92	Up	chr13	hsa-miR-140-5p	97.50	Down	chr16
hsa-miR-1281	177.19	Up	chr22	hsa-miR-193a-5p	73.05	Down	chr17
hsa-miR-1539	169.23	Up	chr18	hsa-miR-34a-3p	61.13	Down	chr1
hsa-miR-125a-3p	159.16	Up	chr19	hsa-miR-432-5p	60.05	Down	chr14
hsa-miR-4271	158.48	Up	chr3	hsa-miR-204-5p	56.88	Down	chr9
hsa-miR-550a-5p	156.32	Up	chr7	hsa-miR-485-3p	55.67	Down	chr14
hsa-miR-642b-3p	142.71	Up	chr19	hsa-miR-140-3p	55.23	Down	chr16
hsa-miR-23c	134.49	Up	chrX	hsa-miR-409-5p	54.21	Down	chr14
hsa-let-7f-1-3p	108.08	Up	chr9	hsa-miR-146a-5p	52.69	Down	chr5
hsa-miR-874	96.40	Up	chr5	hsa-miR-423-5p	50.69	Down	chr17
hsa-miR-33b-3p	88.74	Up	chr17	hsa-miR-17-3p	50.49	Down	chr13
hsa-miR-3180-5p	76.65	Up	chr16	hsa-miR-487a	47.24	Down	chr14
hsa-miR-150-3p	65.94	Up	chr19	hsa-miR-450a-5p	47.14	Down	chrX
hsa-miR-129-1-3p	64.80	Up	chr7	hsa-miR-138-2-3p	45.41	Down	chr16
hsa-miR-1249	63.67	Up	chr22	hsa-miR-128	44.19	Down	chr2
hsa-miR-3679-3p	60.74	Up	chr2	hsa-miR-28-5p	43.34	Down	chr3
hsa-miR-767-3p	34.07	Up	chrX	hsa-miR-431-5p	43.33	Down	chr14
hsa-miR-3656	3.60	Up	chr11	hsa-miR-146b-5p	43.22	Down	chr10
hsa-miR-221-5p	132.32	Down	chrX	hsa-miR-4317	38.84	Down	chr18
hsa-miR-374b	124.96	Down	chrX	hsa-miR-324-5p	38.47	Down	chr17
hsa-miR-590-5p	122.52	Down	chr7	hsa-miR-370	37.81	Down	chr14
hsa-miR-4306	116.09	Down	chr13	hsa-miR-16-2-3p	22.41	Down	chr3

Chr. chromosome

phosphatidylinositol signaling system, non-small cell lung cancer, aldosterone-regulated sodium reabsorption, Wnt signaling pathway, regulation of actin cytoskeleton, axon guidance, TGF-beta signaling pathway, melanogenesis, basal cell carcinoma, arrhythmogenic right ventricular cardiomyopathy (ARVC), pathogenic *Escherichia coli* infection, circadian rhythm, T cell receptor signaling pathway, B cell receptor signaling pathway, glycosphingolipid biosynthesis, valine, leucine and isoleucine degradation, insulin signaling pathway, Hedgehog signaling pathway, mTOR signaling pathway, RNA degradation, heparan sulfate biosynthesis, one carbon pool by folate, prostate cancer, cell cycle, spliceosome, apoptosis, small cell lung cancer, acute myeloid leukemia, adipocytokine signaling pathway, endometrial cancer, inositol phosphate metabolism, and sphingolipid metabolism in paclitaxel-treated HDP cells, and EGCG-downregulated miRNAs regulated Fc gamma R-mediated phagocytosis, pathways in cancer, MAPK signaling pathway, focal adhesion, regulation of actin cytoskeleton, Wnt signaling pathway, chemokine signaling pathway, axon guidance, TGF-beta signaling pathway, renal cell carcinoma, melanoma, melanogenesis, basal cell carcinoma, ErbB signaling pathway, prostate cancer, Hedgehog signaling pathway, p53 signaling pathway, notch signaling pathway, cytokine-cytokine receptor interaction, Jak-STAT signaling pathway, calcium signaling pathway, T cell receptor signaling pathway, dilated cardiomyopathy, amino sugar and nucleotide sugar metabolism, ubiquitin-mediated proteolysis, pathogenic *Escherichia coli*

infection, small cell lung cancer, valine, leucine and isoleucine degradation, purine metabolism, gap junction, glycerolipid metabolism, Huntington's disease, *N*-glycan biosynthesis, fatty acid metabolism, butanoate metabolism, glioma, long-term depression, cysteine and methionine metabolism, neurotrophin signaling pathway, adherens junction, vascular smooth muscle contraction, insulin signaling pathway, progesterone-mediated oocyte maturation, oocyte meiosis, non-small cell lung cancer, chronic myeloid leukemia, dorso-ventral axis formation, mTOR signaling pathway, phosphatidylinositol signaling system, CAMs, endocytosis, splicesome, endometrial cancer, tight junction, chondroitin sulfate biosynthesis, inositol phosphate metabolism, colorectal cancer, GnRH signaling pathway, ECM-receptor interaction, Fc epsilon RI signaling pathway, ABC transporters, neuroactive ligand-receptor interaction, aldosterone-regulated sodium reabsorption, propanoate metabolism, natural killer cell-mediated cytotoxicity, B cell receptor signaling pathway, vascular endothelial growth factor (VEGF) signaling pathway, and pyrimidine metabolism in paclitaxel-treated HDP cells.

Discussion

Therapeutic effect of paclitaxel on tumor cells is reported in many different cancers (Sunters et al. 2003; Millenbaugh et al. 1998; Ettinger 1993). However, paclitaxel also affects other normal cell and then occurs a lot of side effects (Chon et al. 2012). Especially, paclitaxel-induced hair loss, one of the paclitaxel side effects, is caused by the apoptotic damage in HDP cells, one of the key players to form hair follicle and grow hair (Chen et al. 2011). EGCG extracted from green tea has been shown as effective anti-cancer agent and antioxidation agent in normal cells (Hsu 2005; Wang and Bachrach 2002; Hsu et al. 2003). In addition, EGCG is attenuated in cisplatin-mediated HDP cell death (Hsu et al. 2003). Thus, we showed effects of EGCG in paclitaxel-mediated HDP cell death. In this study, to determine regulation of miRNAs by EGCG in paclitaxel-exposed HDP cells, we showed the EGCG-mediated alteration of miRNA profile in HDP cells treated with paclitaxel.

Firstly, we showed that EGCG repressed paclitaxel-mediated growth arrest and cell death in HDP cells (Figs. 1 and 2). In the same condition, we analyzed miRNA profile, since, in recent study, HDP cells regulate cellular signal pathway, such as survival, death, and cell cycle arrest (Kim et al. 2014; Cha et al. 2014). As shown in Figs. 1 and 3, 48 miRNAs have confirmed the EGCG-mediated upregulation or downregulation in paclitaxel-treated HDP cells. In significantly up- and downregulated miRNA, miR-129-1-3p (64.8-fold upregulation) is reported as repressor of PDCD2 which is overexpressed in proliferation of human gastric cancer (Du et al. 2014) and miR-128 (44.19-fold downregulation) was reported to inhibit cell growth, when overexpressed in head and neck squamous cell carcinoma (Hauser et al. 2015). Additionally, EGCG-regulated miRNAs targeted *FOXO1*, *BCL2L1*, *BCL2L2*, *PTEN*, *BBC3*, and *MDM2* which are the regulator genes against cell growth, proliferation, and cell death. When FOXO1 is overexpressed, cell proliferation and growth is inhibited by upregulating caspase-3 and caspase-9 and inducing G2/M arrest and (Yang et al. 2015). BCL2L1 and BCL2L2, BCL2 family, are pro-oncogene and repress intrinsic pathway-mediated cell death (Denoyelle et al. 2014; Zhang et al. 2015). Other genes, PTEN, BBC3, and MDM2, also rescue cell death and induce proliferation (Fortunato et al. 2014; Zhang et al. 2010).

In KEGG pathway analysis against target genes, we find upregulated miRNA-related 58 KEGG pathways and downregulated miRNA-related 68 KEGG pathways. Among these KEGG pathway, Wnt signaling pathway, pathways in cancer, MAPK signaling pathway, and basal cell carcinoma, adherens junction is highly related with upregulated miRNA. And MAPK signaling pathway, neurotrophin signaling pathway, melanogenesis, axon guidance, Wnt signaling pathway are most related to downregulated miRNAs. MAPK signaling pathway and Wnt signaling pathway related to both up- and downregulated miRNAs are involved in cell survival and apoptosis (Zhang et al. 2010; Shang et al. 2015). Thus, we suggest that EGCG-mediated miRNA expression change regulates cell survival and apoptosis through MAPK signaling pathway and Wnt signaling pathway.

Following our results, we demonstrate that EGCG-regulated alteration of miRNA expression increase proliferation and decrease cell death in paclitaxel-treated HDP cells. Additionally, these results suggest that EGCG reduced paclitaxel-mediated hair loss by alteration of miRNA profile.

Conclusions

This is the first study to address positive effects of EGCG in paclitaxel-mediated hair loss. The study demonstrated that EGCG increases proliferation, decreases cell death by alteration of miRNA profile in HDP cells, and sequentially affects paclitaxel-mediated hair loss.

Additional file

Additional file 1 Table S1. Predicted targets of miRNAs upregulated in response to EGCG treatment in HDP cells. Table S2. Predicted targets of miRNAs downregulated in response to EGCG treatment in HDP cells. Table S3. Main functions of upregulated miRNAs predicted by

bioinformatics analysis. Table S4. Main functions of downregulated miRNAs predicted by bioinformatics analysis. (DOCX 76 kb)

Abbreviations
ARVC: Arrhythmogenic right ventricular cardiomyopathy; CAMs: Cell adhesion molecules; DMEM: Dulbecco's modified Eagle's medium; EGCG: Epigallocatechin-3-gallate; FACS: Fluorescence-activated cell sorting; FBS: Fetal bovine serum; HDP: Human dermal papilla; KEGG: Kyoto Encyclopedia of Genes and Genomes; MAPK: Mitogen-activated protein kinase; miRNA: MicroRNA; PBS: Phosphate-buffered saline; PI: Propidium iodide; UTR: Untranslated region; VEGF: Vascular endothelial growth factor; WST-1: Water-soluble tetrazolium-1

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Availability of data and materials
Not applicable

Authors' contributions
SHS, HJC, and KK conducted the study and drafted the manuscript. All authors analyzed the data and reviewed the literatures. SHS and SA wrote the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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