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Intravenous Photo Dynamic Therapy (PDT) with Liposome-ICG for Possible Tertiary Cancer Prevention by Epigenetic Effects

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Abstract

We performed Photo Dynamic Therapy using liposome-ICG (indocyanine green) in the peripheral blood of the two patients (Patient X and Patient Y, hereafter), both of whom had recovered from cancer. Patient X, with cervical cancer, received hysterectomy three years ago and Patient Y with gastric cancer had Endoscopic Submucosal Dissection (ESD) 6 years ago. One week before and after PDT, whole RNA sequences and quantification of the monocytes isolated from their blood were examined. Correlated expressions of highly increased or decreased in RNAs were: increases in FAM156B, PHLDA2, NME1-NME2 and decreases in TRIM49D2, FRI3-ITI, LOC100133050 and FAM186B). All the increased RNAs revealed anti-oncogenic properties and all the decreased ones revealed oncogenic properties. As most of these RNAs are regulated by methylation, the PDT therapy may serve to epigenetically lower the risks of cancer.

Keywords: Methylation • Liposome-icg • Non-coding RNA • Epigenetics

Introduction

PDT is one of the therapeutics used for various cancers including head and neck malignancies [1]. ICG (indocyanine green) a photo sensitizer, produces singlet oxygen which is toxic to cells [2] when irradiated by laser light at 600-800 nm. Nanoparticles such as a liposome when they include ICG can cause EPR effect and are preferentially absorbed into cancer cells [3]. Circulating Tumor Cells (CTC, hereafter) are hard to find even at the end stage of cancers but some CTCs that associate with white blood cells may exist even in the blood of apparently healthy persons [4-6]. With a view to developing a measure to lower invisible cancer risks, we performed PDT with liposome-ICG (PDT, hereafter) on two apparently healthy patients who experienced cancers [7-9].

Case Presentation

Patient X was a 72- year-old woman who was diagnosed with stage IB cervical squamous carcinoma and received total hysterectomy 3 years ago. Patient Y was a 71-year-old man who was diagnosed with early gastric cancer (highly differentiated adenocarcinoma) and received ESD (Endoscopic Submucosal Dissection) 6 years ago.

Methods

RNA extraction: Prior to PDT 7.5 ml of blood was collected from each of the two patients and the buffy coat cells were obtained by Percoll™ following the specified manual and the cells were frozen and stored at -80 in 0.5 ml of RNA later until RNA extraction was performed. One week after PDT, buffy coats were collected again from the two patients and frozen at -80 in the same manner. RNAs were extracted from the four samples for sequencing and quantification.

PDT with liposome-ICG (PDT): Ten mg of ICG (Fujifilm, Japan) was mixed in 10 ml of Liposome (Hybrid vector, State Art, Japan) and was infused to the patients by a peripheral retention catheter. One day after infusion irradiation at 620 nm was performed by LED light (MLDS™, Multi-Laser Delivery System) at 100 mW for one hour.

Data analysis: Data analyses were performed by two companies i.e., Macrogen and Cell Innovator, Japan. From about 20,000 normalized RNAs data, those with a p-value of less than 0.05 and higher/lower than 1.0/-1.0 of comparative log 2 FC were selected to examine the differences between before and after PDT.

Results

To assess the potentials of PDT to be utilized for cancer prevention, we performed the whole RNA sequencing and quantification of buffy coat cells from the two cancer survivors before and after PDT; increased and decreased values were 2d-plotted as shown in the (Figures 1 and 2), respectively. Among the crossed data between gastric and cervical cancer patients, the same level of and large scale of corresponding points (diagonal axis) were observed in the two cancer survivors, indicating cancer-preventive effects of PDT. Increased correlated values are labeled (FAM156B, PHLDA2, NME1-NME2) in (Figure 1) and decreased ones (TRIM49D2, FRI3-ITI, LOC100133050 and FAM186B) in Figure 2.

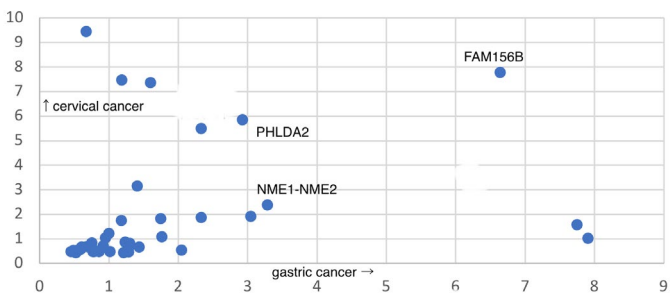

Figure 1. Up-regulated RNAs both in patient Y with gastric cancer and patient Y with cervical cancer. Labels are assigned on the three highly up-regulated and correlated RNAs.

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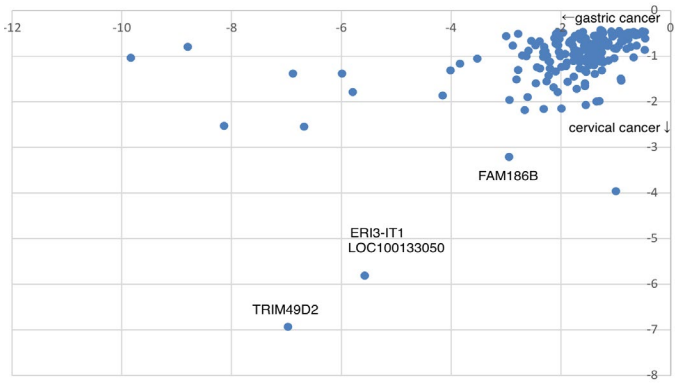

Figure 2. RNAs decreased both in patient X with cervical cancer and patient Y with gastric cancer. Labels are assigned on the three highly down-regulated and correlated RNAs.

RNAs highly increased and correlated in Patient X with cervical cancer and Patient Y with gastric cancer

FAM156B: FAM156B (located at Xp11.22) belongs to the transmembrane proteins' (TMEMs) family. Many genes are located on the X chromosome playing a vital role in cancer development [10]. Quite a few human transmembrane families of genes such as TMEM- 176A, TMEM- 176B, TMEM- 119 and TMEM- 25 are reported to be hyper-methylated and their mRNAs are down-regulated. Abnormal methylation of TMEMs is associated with risks of various cancers including lymphomas, gastric carcinoma and CRC [11]. TMEM25 is methylated and also down-regulated in colorectal cancer [12]. Methylation of FAM156B gene and mRNA down-regulation in WBC are strongly associated with increased CRC risk [13]. Though we performed no examination of methylation state, FAM156B of Patient X and Patient Y were up-regulated as shown in Fig. A, which suggested a possibility of PDT-ICG demethylating from FAM156B gene, resulting in increased FAM156B. Thus, PDT was considered to have potential to lower cancer risk.

PHLDA2: PHLDA2 (lacustrine homology-like domain family A member 2) is located in a cluster of imprinted genes on chromosome 11p15.5, which is considered to be a powerful tumor suppressor region. PHLDA2 regulates EMT and autophagy in colorectal cancer *via* the PI3K/AKT signaling pathway [14] and its overexpression inhibits AKT phosphorylation and suppress tumor development. Thus, increase of PHLDA2 after PDT, shown in Fig. A, was considered to reveal PDT's potential to prevent cancer progression.

NME1 and NME: NME1-NME2 are Nucleoside Diphosphate Kinases (NDPKs) and regulate tumor cell endocytosis, motility and metastasis [15,16]. Overexpression of NME1-NME2 in cancer cell lines are known to increase endocytosis of transferrin and EGF receptors concurrent with motility and migration suppression. Thus, increase of NME1-NME2 after PDT, shown in (Figure 1), was considered to show PDT's potential to prevent cancer metastasis (Figure 1).

RNAs highly decreased and correlated in Patient X with cervical cancer and Patient Y with gastric cancer

TRIM49D2: TRIM49D2 (Tripartite Motif Containing 49D2) is high in endometrial carcinoma [17] and ovarian cancer [18]. As shown in (Figure 2), decrease in TRIM49D2 was observed after PDT, indicating possibility of its preventing cancer promotion.

ERI3-IT1: ERI3-IT1 (ERI3 Intronic Transcript 1) is affiliated with the lncRNA class. ERI3-IT1 is an exoribonuclease Family Member 3-IT1 is high in osteosarcoma [19]. As shown in (Figure 2), decrease in ERI3-IT1 was observed after PDT, indicating possibility of its preventing cancer promotion.

LOC100133050: LOC100133050 is hypomethylated at the promotor and the mRNA is over-expressed in the triple negative breast cancer [20]. As shown in (Figure 2), mRNA was under-expressed after PDT, indicating possibility of its lowering risk of cancer occurrence.

Fam186b: Though no exact function of Fam186b is known, it can be a TPRKB interactor identified through Immunoprecipitation/Mass-Spectrometry in U2OS cells over expressing MDM2 [21]. As shown in (Figure 2), decrease of Fam186b was observed after PDT, indicating its potential to prevent cancer promotion (Figure 2).

Discussion

In Japan, one in two people suffers from cancer and one in three cancer patients dies from it, reportedly. Early detection is crucial for recovery and prevention of recurrence. Though assessment of genetic and environmental factors involved in cancer development accompanied by contemporary liquid biopsy of circulating tumor cells/DNAs is a hallmark for cancer detection, it is not yet ensured [4-6]. Esophageal cancer, a solid tumor, can be diagnosed at an approximate 80% of accuracy by a CTC test on peripheral blood cells [22]. We performed PDT on similarly obtained peripheral cells and among resultant differentially expressed RNAs, oncogenic RNAs decreased after PDT and anti-oncogenic RNAs increased after it. Differences of RNAs expression before and after PDT strongly suggests that PDT lowered risks of cancer recurrence of the two patients. Among large scale and correlated RNA expression of gastric and cervical cancers, a long non- coding RNA such as LOC100133050 is possibly hyper-methylated at promotor region and down-regulated. While promotors of FAM156B and PHLDA2 may be hypo-methylated, RNAs are up-regulated. Thus, PDT is likely to have produced epigenic effects such as ECT (Electroconvulsive therapy) response [23]. Effects of PDT with ICG to epigenics are described [24-26].

Conclusion

While our study represents a significant step forward in exploring PDT as a diagnostic and therapeutic tool, further research with larger cohorts is warranted to validate our findings and better understand the full extent of PDT's epigenetic effects. Ultimately, the potential of PDT to lower cancer recurrence risks and improve outcomes offers a beacon of hope in the ongoing battle against this formidable disease. It underscores the importance of continued research and innovation in the field of cancer diagnosis and treatment.

Acknowledgement

None.

Conflict of Interest

No potential conflict of interest was reported by the authors.

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