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Radiotherapy is One of the Effective and Common Measures of Pancreatic Cancer Therapy: Iodine-125 (125i) Brachytherapy Improves Local Control and Increase Survival

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Abstract

Introduction: The malignant tumors of torment and life taking pancreatic cancer account for adeno-carcinoma which finds its origin in the exocrine secretions of pancreas. Though a lot many techniques and methodologies are surfacing in the field of medical science but still the overall survival rate is not remarkable. The recommended treatment for local tumor control is the implantation of the I125 radioactive seed (brachytherapy) in the effected organ.

Objective: This study was carried out in order to reveal the individual and synergistic efficacy of I125 and ING4 for the treatment of pancreatic cancer tumors. Both *in vitro* (pancreatic cell lines) and *in vivo* (in mouse model) investigations were performed.

Material and methods: The vibrant combination of ING4 and radiotherapy with I125 for treating pancreatic cancer had been done before this appraisal unknown. We investigated that whether ING4 and I125 radiotherapy treatment can suppress Panc-1 pancreatic cancer cell tumor growth or not using *in vitro* and *in vivo* substrates.

Results: In this study, we demonstrated that either ING4 or (125)I radiotherapy treatment could induce Panc-1 pancreatic cancer cell growth suppression and apoptosis *in vitro*. The outcomes revealed that both treatments inhibited can inhibit the malignancy of pancreatic cancer with their tumor suppressive functions. Hence (*ING4*) gene therapy plus (I125) radiotherapy had produced synergistic effects.

Introduction

The malignancy of pancreatic tissues is chronic and even becomes acute in severe cases. This very rapidly growing carcinoma aggressively spread in pancreas of human body and may sometimes take entry into nearby organs in shape of secondary cancer if not properly treated on time. If we look in the recent history of human death rate the devastations of pancreatic cancer are significant. Early prognosis can reduce the devastating effects of pancreatic cancer. Although medical science has devised various therapeutic treatment options and techniques for pancreatic cancer but unfortunately the outcomes are disappointing. Even the combined treatments of external beam radiotherapy (EBRT) and chemotherapy have shown unsatisfactory results for the prognosis of pancreas malignancy. 90% alarming mortality rate has been reported by this menace [1].

It is worthwhile to mention here that the cancerous pancreas is rarely transformed to healthy organ with the deployment of conventional surgical and chemotherapeutic treatments. Similarly nearly 20% patients get long and eventual cure [2,3]. The need of time is to introduce new innovative therapeutic techniques for the rest of the lot suffering from the same painful ailment [4]. Gastric bypass has somehow palliative effects upon malignant pancreas as it increases chances of survival for the patient up to half a year [5,6].

Since radiotherapy is commonly used method for curing cancer disease along with surgical treatment and chemotherapy for the purpose of subjecting only cancerous organ with great precision the targeted dose of radiations are conformed as blocking techniques for tumor. Computerized imaging has helped a lot in shielding the local healthy organs from high dose and effects of radioactive beam [7]. However the transformations in the shape or size during treatment phase can be governed precisely by the means of adequate, appropriate and advanced radiation therapy techniques. This is because the radiotherapy delivers the required dose for the malignant tissues leaving very little exposure to the nearby healthy tissues [8]. With the advancement radiology these radiations are either given outside in (EBRT) or inside out (Brachytherapy). Treating cancer tumor from inside is effective for only delivering radiation to the targeted mass of the affected organ [9].

Radiotherapy increases the probability of controlling the tumor size and its threats. Four-dimensional imaging assists the radiologist to restrain radiations only within the affected cancerous organ. Similarly, the effectiveness of radiotherapy is relevant to the dose of exposure given to the organ and response that is being shown by that very specifically subjected organ [10]. In this regard various advancements in the radiotherapy technique are evident for increasing the survival

rate of patients suffering from pancreatic cancer. Sometimes the conglomeration of radiotherapy, chemotherapy and biologically targeting are used to enhance OS (overall survival rate) of the cancer affected individuals [7]. But all the techniques go in vain if the tumor recurs [7]. In response to such difficulty and challenging situations there is an imperative need to provide optimum dose of radiation for targeting the unhealthy organ in order to avoid the recurrence of cancer [7].

For the improvement after the prognosis of cancer various adjuvant treatments are used in combination with radiotherapy in order to inhibit recurrence [11,12]. Debates are still surfacing in field of medical science for the effectiveness of irradiation therapies given to the subject externally for pancreatic carcinoma [13,14].

The research conducted by Minsky et al. revealed the fact that External beam radiotherapy therapy (EBRT) plus chemotherapy are extensively suggested by the radiologists to the pancreatic cancer patient. In combination of these two therapies sometimes intraoperative electron beam radiotherapy is also used but unsatisfactory outcomes are found [15-19]. Though this combination relieves pain to the significant level but has severe effects on patient's body and increase only median survival rates. The OS (overall survival rate) is very less in case of using Also EBRT alone [20,21]

The victims with loco-regional recurrence of cancer may be treated with conventional cancer treatments or with EBRT [22,23] but as an alternative and effective treatment for rapidly growing pancreatic cancer the Brachytherapy with Iodine-125 is widely used nowadays. This therapy has minimal side effects for the healthy volume of the organ [24].

Basically brachytherapy is permanent implantation of radioactive seeds are useful for controlling localized tumors of pancreatic carcinoma in the treatment of pancreatic cancer [25-28]. Radioactive iodine-125 seed implantation has shown good results for treating respectable pancreatic carcinoma [29-31]. The interesting thing about brachytherapy is that the dose for the targeted volume of the cancerous tissues can be increased by placing radioactive seed inside the targeted organ and then subjecting it with the emission of stable and quick gamma rays. During this localized and targeted radiation the dose of radiation is of low energy (e.g iodine-125 seed) hence minimizing the impacts on surrounding tissues.

Since brachytherapy is targeted so its remains unaffected by the boy posture, motion, respiration and other interferences. Not only pancreatic cancer is treated with this therapy but other chronic cancers like head, neck and pulmonary carcinoma etc. are also cured [32-36].

Iodine-125, iridium-192 or palladium-103 seeds are mostly used in brachytherapy to be implanted inside the malignant tissue. But out of these commonly used seeds iodine-125 seed is the most recommended one because half-life of this radioactive element reaches upto 59.7 days. In contrast to high energy radioactive seed like radium-226 the low-energy iodine-125 seeds are successively used form the last 30 years [37] hence significantly reduces chance of tumor recurrence and controlling growth of pancreatic carcinoma [38]. Moreover brachytherapy with Iodine-125 seed treatment is an effective remedy for getting marked response from malignant tumor and it is being used from many years [39]. Brachytherapy combined with other adjuvant therapy for treating cancer did not show successful results [40].

Material and Methods

The Quick Change Site-Directed Mutagenesis Kit (Strata gene, La Jolla, CA) was used to generate mutant versions of ING4; with the help of the complementary DNA of the human ING4 protein, which used the retroviral vector Plpc (variant v1;24) as a template for cloning purpose Figures 1 and 2.

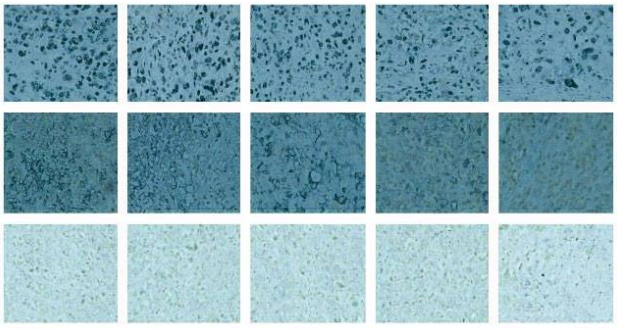

Figure 1: Adenovirus-mediated ING4 expression; Panc-1 cells were treated with PBS, Ad-GFP, Ad-hING4, 125I, and Ad-hING4 plus 125I and were observed with fluorescence and differential interference contrast (DIC) microscopy.

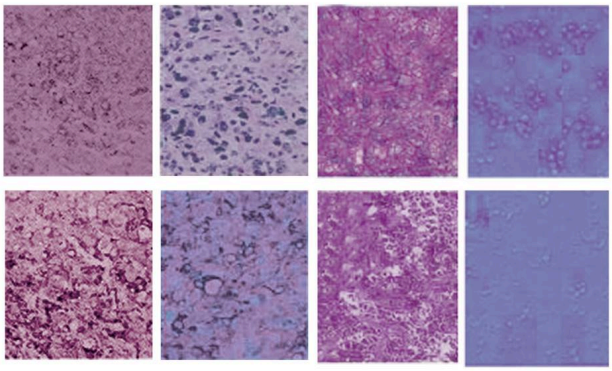

Figure 2: Inhibition assay of tumor growth *in vivo*; The morphological observations of tumor tissues in different groups.

PCR *via* Pfu Turbo DNA polymerase (strata gene) was used to incorporate specific mutations. DpnI was subsequently used to splice the methylated parental band. These fragments thus formed, were verified with the help of gene sequencing. Overall all Panc-1 cells were divided in three main groups in their log growth phase;

Two experimental groups (AdING4, AdING4 plus I125 group)

Negative control group Ad-Green Fluorescent Protein or AdGFP group

Two cell control group I125 and PBS group

In vitro investigation

In vitro study was conducted by keeping the temperature at 37°C, during plate culture for each group. All cultured plates were observed

under high resolution fluorescent microscope and with DIC (differential interference contrast).

In vivo investigation

Similarly, for *in vivo* investigations, 10 nude mice (divided in five groups i.e. two mice per group) were taken and injected with the aforementioned solutions. The tumor growth for both studies (*in vivo and in vitro*) was recorded and observations thus made were as follows:

Results

Morphological investigations in Panc-1 infected cells

Panc-1 were introduced to doses of 100 MOI of AdING4, I125 and AdGFP (10^9 pfu/mL) for 72 h. Upon investigation of morphological changes in these infected cells (fluorescent light microscope), it was observed that under the conditions of AdGFP and PBS solutions, the cells retained their structure and growth quite well. Whereas, those introduced to AdING4 cultures exhibited significant abnormalities in both structure and adherence (which were reduced significantly). In addition the cells introduced to AdING4 and AdGFP showed remarkable green fluorescence.

Inhabitance of growth

The significant inhibition in growth rate was observed in Panc-1 cells in the culture plates containing AdING4. The rate of inhibition was about 50-60% within 4 to 5 days of observation (<0.05). The results showed that *AdING4* gene can inhibit the growing Panc-1 cells.

Presence of apoptosis

Those Panc-1 cells which were subjected to I125, AdING4 plus I125 AdING4 after staining showed the clear indications for apoptosis (condensation and beak down of nucleus). However, the percentage of apoptotic cells was significantly higher in the I125 as compared to AdING4 p>0.05. Data shown are representative of three independent experiments. In the remaining groups no apoptosis was detected at all Figure 3.

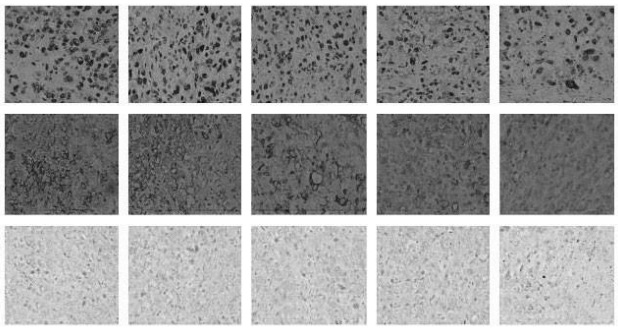

Figure 3: Detection of apoptosis-related molecules in Panc-1 human pancreatic carcinoma s.c.xenografted tumors cells by immunostaining; Representative immune histochemical pictures of Caspase-3, Fas, Bax, Bcl-2 and Survivin in Panc-1 pancreatic carcinoma xenografted tumors.

mRNA transcripts

The Panc-1 cells having 100 MOI AdGFP and AdING4 infection were used to extract the RNA followed by RTPCR in order to read the mRNA transcriptions. There sequence of Bcl2, Bax, p53, Fas, Survivin and Caspase3 were focused. Significantly Bcl2's down regulation was recorded for the cells containing ING4. Along with it the up regulation of *Bax, Caspase3* and *p53* genes was observed for the same cultures Figures 4 and 5.

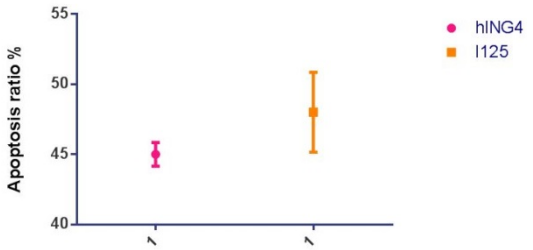

Figure 4: The percentage of apoptotic cells was significantly higher in the 125I as compared to hING4 *p*>0.05 when the Ad group was compared with the PBS group). Data shown are representative of three independent experiments.

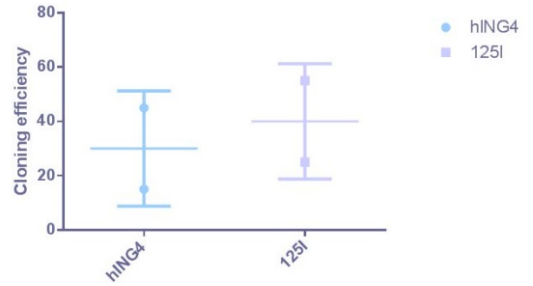

Figure 5: Colony formation assay; Compared with group hING4 with 125I groups. I125 is higher were significantly higher.

Growth rate of tumors

The growth of tumor was observed in all 10 mice belonging to each group. But tumors were limited to the subcutaneous layer. Thereafter the growth was successively increased. Significant slow growth of tumors was achieved in the mice inoculated with I125, ING4 and ING4. In PBS and AdGFP groups the rate of tumor growth was much higher and continuous.

The tumor growth in experimental groups i.e. I125, I125 plus AdING4 and AdING4 was very small compared to the rest of the groups (<0.05). No remarkable change in volumes if tumor was noticed between the controlled and negative control groups (PBS and AdGFP respectively).

Tumor cell physiology

For the clear view some specimens of the tumors were perfectly stained with HE. The expected outcomes were observed. The tumors in I125, ING4 and I125 plus ING4 were having necrosis with the shrinkage, non-cellular appearance and pink fragmentations of cells. Whereas, the tumors in PBS and AdGFP groups had pathologic division of cells.

No significant change in the expression of genes was recorded for controlled and negative controlled groups.

Discussion

The discovery of *ING1* brought the innovation in the world of genetics, opened the doors for the detection of other ING members and isoforms of inhibitors of growth (*ING2-5*) which were associated with cell cycle, apoptosis and senescence [41]. They also consist of the tumor suppressor genes TSG (*ING1, ING2, ING3, ING4 and ING5*) the suppression involves such mechanisms which includes the interactions with the chromatin function and gene specific transcription, these also controls the cell cycles, DNA repair and apoptosis.

Apoptosis is induced by ING4 on the tumor cell virtue with an increased p53 transcription which consequently shortens the S phase of cancer cells and enhances the G2/M phase simultaneously arrest of HepG2 liver cancer cells. Nuclear localization signals and N-terminal sequences are present in the inhibitors of the growth which plays an important role in interacting with histone acetyl transferase (HAT) and histone de-acetyl transferase (HDAC) that helps in regulating the activity in the gene promotion within chromatin [42-44]. ING4 induces tumor cell apoptosis by virtue of an increased p53 transcription which subsequently results in shortening the S phase of RKO colon cancer cells and simultaneously enhancing the G2/M phase arrest of HepG2 liver cancer cells.

Previous studies suggest that the class of ING is capable to regulate those chemical agents that can damage or even destroy the DNA hence it can inhibit the transmission of mutant gene in neighboring cells. ING4 curbs the movement of tumor cell by interaction with liprin α 1 protein [45-48]. All such actions and activities depict the antitumor effects including various mechanisms and pathways (Figure 6).

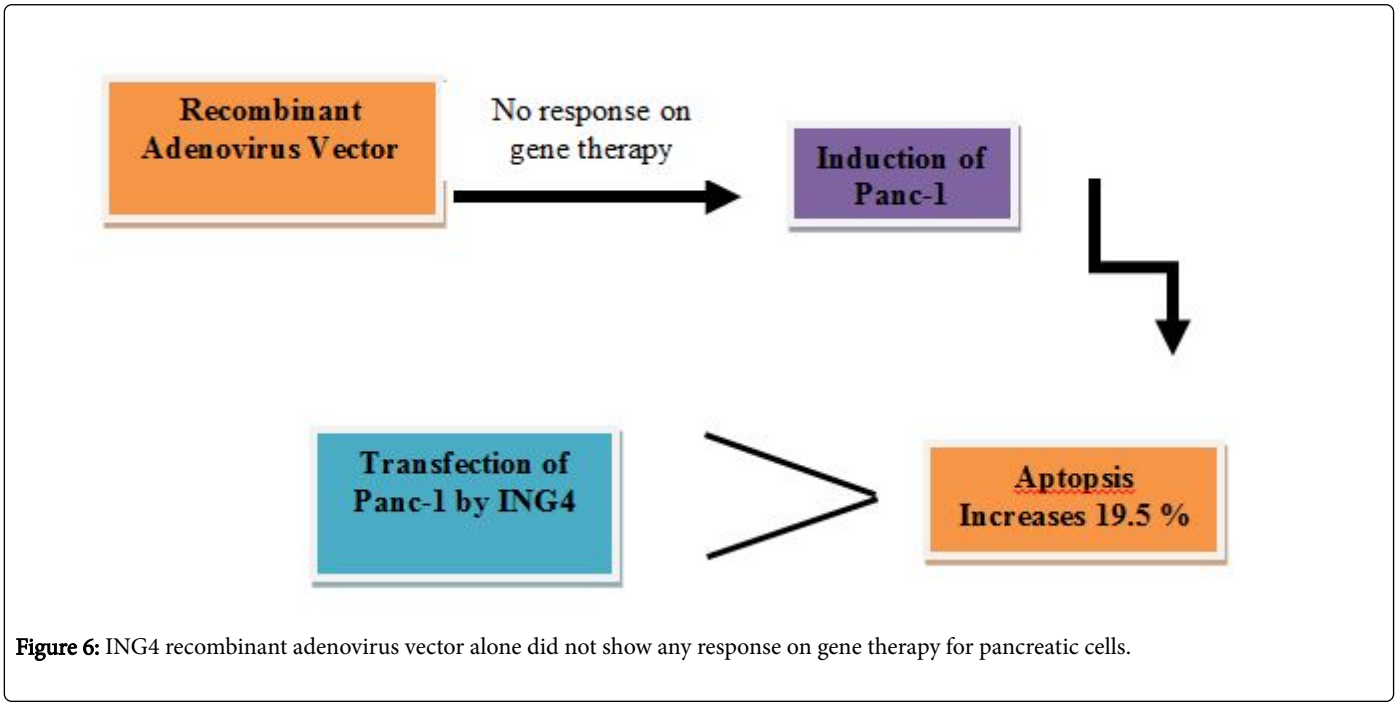

Figure 6: ING4 recombinant adenovirus vector alone did not show any response on gene therapy for pancreatic cells.

ING4 recombinant adenovirus vector alone did not show any response on gene therapy for pancreatic cells. Therefore Panc-1 was introduced in the infected cells *in vitro* with adenovirus for investigation of the individual effects of AdING4 and the associated growth mechanism identification. The gene was successfully transfected into Panc-1 cells by ING4 proved by RTPCR.

The adenovirus induced *ING4* gene expression drastically inhibits the proliferation of Panc-1 cell which enhances apoptosis with 20% rate. That is higher than the (PBS) cell control group [49]. The cells staining and observation was done using Hoechest 33258 laser scanning confocal microscopy. These further supported that AdING4 plus I125 induced cell apoptosis and nuclear morphological changes in Panc-1 cells, whereas no apoptotic nuclear morphological changes in AdGFP and PBS groups were seen. Investigation using RTPCT of the molecular mechanisms of the antitumor effects of *ING4* genes was also conducted. After transfection of *ING4*, the gene promoting apoptosis Bax transcription was up regulated and in the mean while down regulation of anti-apoptosis gene Bcl2 was recorded. Thereafter the ratio Bax:Bc12 becomes higher. Moreover, the increase in the transcription of the tumor suppressor gene *p53* that aids in activation of the Caspase3 causes cleavage of Caspase3. This cleavage is the clear evidence of apoptosis which has been induced to the cancer cell the cleave indicates the enhanced *ING4 p53* transcription, and apoptosis of induced tumor cell by a pathway dependent on p53.

The tumor treatment was also experimented in the nude mice with AdING4 and I125. This combination inhibits the growth rate

completely. These results of experiments signals out that ING4 can inhibit the growth of the transplanted tumor specifically. Massive necrosis regions were seen in the mice after the use of AdING4, I125, AdING4 plus I125 whereas negative control groups still consisted the tumor cells having mostly cells in the mitotic phase. The numerical scale of apoptotis of AdING4 group was importantly higher than in the AdGFP and PBS control groups.

The up regulation of *Bax* gene in the antitumor effect of AdING4 and down regulation of *Bcl2* gene activates the Caspase3 pathway results in the apoptosis. A Vitro study also produces the consistent behavior. This study proves the experimental evidence which supports the possibilities of the gene therapy for the treatment of pancreatic cancer with the combination of I125 plus AdING4. This combination increases the survival rate of the people having pancreatic ailment. Therefore, as compared to the individual effects of ING4 and I125 their synergistic effects for the tumor growth inhibition are much more useful to reduce the mortality rate of pancreatic cancer.

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