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The Novel Use of IL-28 as an Effective Radiosensitizer in Pancreatic Cancer

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Abstract. *Background/Aim: Pancreatic cancer is the second most common gastrointestinal cancer in the world, yet the five-year survival outcome rate of less than 5% urges for improvement in medical interventions of pancreatic cancer. Currently, high dose radiation therapy (RT) is used as an adjuvant treatment; however, the high level of RT required to treat advanced neoplasms leads to high incidence rates of side effects. In recent years, the utilization of cytokines as radiosensitizing agents has been studied, in order to reduce the amount of radiation required. However, few studies have examined IL-28 regarding its potential as a radiosensitizer. This study is the first to utilize IL-28 as a radiosensitizing agent in pancreatic cancer. Materials and Methods: MiaPaCa-2, a widely used pancreatic cancer cell line was used in this study. Clonogenic survival and cell proliferation assays were used to evaluate growth and proliferation of MiaPaCa-2 cells. Caspase-3 activity assay was used to evaluate apoptosis of MiaPaCa-2 cells and RT-PCR was used to study the possible molecular mechanisms. Results: Our results showed that IL-28/RT enhanced RT-induced inhibition of cell proliferation and promoted apoptosis of MiaPaCa-2 cells. Furthermore, compared to RT alone, we found that IL-28/RT up-regulated the mRNA expression of TRAILR1 and P21, while down-regulating mRNA expression of P18 and survivin in MiaPaCa-2 cells. Conclusion: IL-28 has the potential to be used as a radiosensitizer for pancreatic cancer and warrants further investigation.*

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Pancreatic cancer causes over 400,000 deaths annually (1). Traditional intervention for pancreatic cancer involves chemotherapy alongside radical resection for significantly increased survival (2). Radiation therapy is typically used for locally advanced cancer. However, it has been found that standard doses of radiation tend to have little effect on patient survival in such advanced neoplasms (3). Ablative radiation, rather, relies on higher doses for achieving greater patient survival. Yet, increased radiation dosage comes with higher incidence of side effects, such as skin irritation, pain, fatigue, weight loss, heightened infection risk, and others (4). As such, there is interest in discovering radiosensitizers that minimize radiation dose while maintaining therapy effectiveness.

There is a large body of literature providing evidence for the efficacy of interleukins as radiosensitizing agents (5-8). Our laboratory is currently studying various cytokines, including IL-28, for their role as radiosensitizers to reduce the dosage of radiation and thereby lower the propensity for adverse effects of treatment. We have previously found potential radiosensitizing properties in IL-37 and IL-21 (5, 9).

IL-28 was first identified in 2003 (10). It is a member of the type 3 interferon family, similar to IL-29, with some similarities to the type 1 IFN family (11). Like all cytokines, IL-28 plays a role in the adaptive immune response against microbial infection. In the human genome, it is located on chromosome 19. There are multiple isoforms, including IL-28A and IL-28B (12). IL-28 appears to have anti-cancer

effects in bone metastatic prostate cancer, fibrosarcoma, and pancreatic cancer without radiation therapy (13-15). However, at the time of writing this article, there are no studies that utilized IL-28 specifically for use in radiation therapy on pancreatic cancer cells. This study investigates whether IL-28 contributes to anti-proliferation and/or pro-apoptosis of pancreatic cancer cells during exposure to radiation.

Materials and Methods

Tumor cell line. The human MiaPaCa-2 cell line used in this study was provided by Dr. Citrin from the Radiation Oncology Branch of the National Institutes of Health (Center for Cancer Research, National Cancer Institute, MD, USA). MiaPaca-28 cells were cultured in Dulbecco's modified Eagle's medium (Invitrogen, Carlsbad, CA, USA). A solution of 10% heat-inactivated fetal bovine serum and 1% penicillin-streptomycin (Invitrogen, Waltham, MA, USA) were used to supplement the medium as previously described (16). Treatment options were performed once MiaPaCa-2 cells reached 70% confluence.

Treatment of pancreatic cancer cell line with IL-28. After reaching 70% confluence, the MiaPaCa-2 pancreatic cancer cells were treated for 3 days with one of the following: IL-28 (50 ng/ml, Shenandoah Biotechnology, Warminster, PA, USA) or DMEM medium (Invitrogen, Carlsbad, CA, USA) alone. The concentration and incubation time for the treatments was established from our prior cytokine studies (5, 17).

IL-28 and radiation therapy (RT) of pancreatic cancer cell. Seventy percent confluent MiaPaCa-2 cells were treated with IL-28 (50 mM) for 24 h, followed by RT at 4 Gy, or with a mock treatment. The external beam radiation therapy (XRT) was based on our previous studies (5,17). All RT was carried out using the XRAD 320 Biological Irradiator (Precision X-ray, North Brandford, CT, USA) at 320 Kv, 12.5 mA, and 50 cm focus-to-surface distance with filter 1 (280 cGy/min); cells were irradiated at room temperature in 75 cm2 culture flasks (5, 17). Cells were then cultured for 24 h for analysis studies and 72 h for apoptosis studies.

Clonogenic survival assay. A clonogenic survival assay was performed for 4 treatment groups: control (Cx), radiation alone (RT), IL-28 alone (IL-28), and radiation with IL-28 (IL-28/RT). After 3 days of incubation, MiaPaCa-2 cells were detached and counted with a hemocytometer. Clonogenic survival assay was performed as previously described (17). The number of treatment colonies were expressed as a percentage of total control colonies.

Quick cell proliferation assay kit. A quick cell proliferation assay kit by BioVision (Milpitas, CA, USA) was used to measure cell proliferation, according to the manufacturer's protocol. Cell content of the samples was determined by metabolic activity with the use of formazan dye for spectroscopy (18).

Measurement of Caspase-3 activity. Caspase-3/CPP32 colorimetric assay kit by Biovision was used to calculate the apoptosis of MiaPaCa-2 cells by measuring cellular caspase-3 activity (18).

Reverse transcription-polymerase chain reaction (RT-PCR). In preparation for RT-PCR, the MiaPaCa-2 pancreatic cancer cells were washed with a phosphate-buffered saline, homogenized in TRIzol (Invitrogen), and then underwent RNA extraction. As previously reported, 1 μg of RNA underwent reverse transcription (18). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was utilized as the internal control.

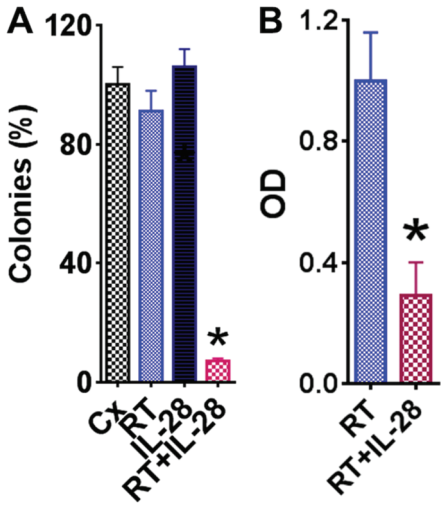

Figure 1. *Effect of IL-28/RT on growth of MiaPaCa-2. (A) MiaPaCa-2 pancreatic cancer survival decreases (p<0.05) upon exposure to IL-28/RT, as measured by the clonogenic assay. (B) MiaPaCa-2 pancreatic cancer proliferation decreases (p<0.05) upon exposure to IL-28/RT, as measured by OD. Student t-test and/or ANOVA were used. Statistical significance in the difference between the radiation (RT) and IL-28/RT groups is denoted by the star symbol (*) (p<0.05).*

Statistics. All experiments were repeated three times. Statistical analysis was conducted using an unpaired two-tailed Student's *t*-test and/or ANOVA. A *p*-Value <0.05 was considered significant.

Results

IL-28 sensitizes MiaPaCa-2 cells to RT. We investigated if IL-28 could sensitize MiaPaCa-2 cells to RT. MiaPaCa-2 colonies were compared under conditions of RT alone, IL-28 alone, and IL-28/RT. We found that RT alone and IL-28 alone did not significantly affect the growth of MiaPaCa-2; however, combination of IL-28 and RT significantly reduced colony size by 90% (Figure 1A). This significant difference of mean optical density (OD) + standard error of the difference (SED)between the RT and the IL-28/RT group suggests that exposure to IL-28 prior to RT effectively reduced pancreatic cancer cell survival (Figure 1B). These results suggest that IL-28 has synergistic effect with RT on inhibiting the growth of MiaPaCa-2 cells.

IL-28/RT alters the expression of pro- and anti-proliferative molecules in MiaPaCa-2 cells. To explore the potential molecular mechanisms by which IL-28/RT inhibits the growth

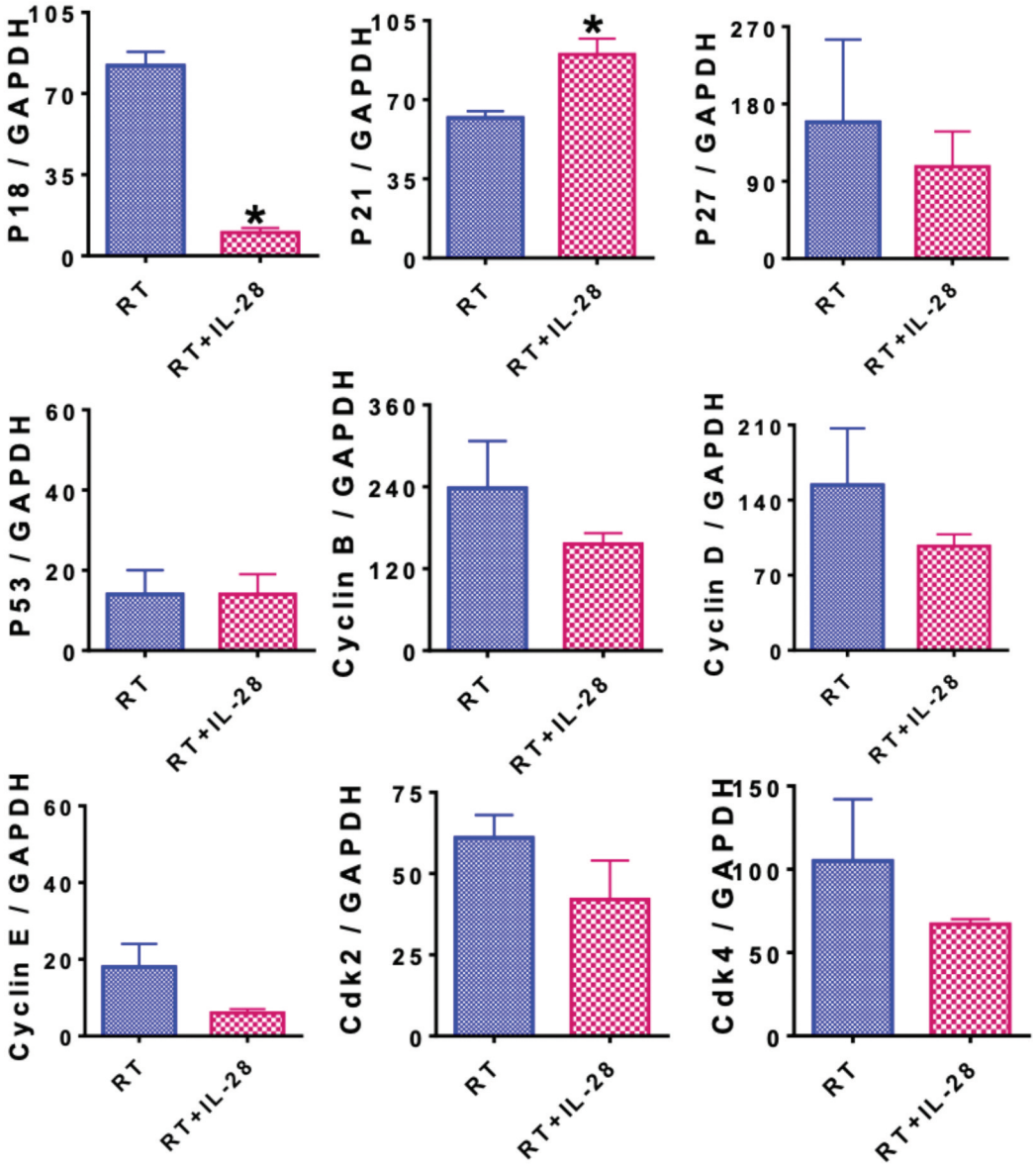

Figure 2. *Effect of IL-28/RT on expression levels of pro- and anti- proliferative molecules in MiaPaCa-2 cells evaluated by RT-PCR. Results are expressed as the mean ratio of proliferative molecule densitometric units/GAPDH (n=3). Error bars indicate standard error of the mean (SEM). *p<0.05 using Student's t-test.*

and survival of MiaPaCa-2 cells, mRNA expression of major anti- and pro-proliferative molecules in MiaPaCa-2 cells was determined by RT-PCR after treatment with RT alone or IL-28/RT. We tested molecules that are essential factors of cellular proliferation: P18, p21, P27, P53, Cyclin B, Cyclin D, Cyclin E, Cdk2, and Cdk4. Out of those molecules, there was a marked increase in the expression of the anti-proliferative molecule P21 and reduction of the pro-proliferative molecule P18 (Figure 2). Additionally, there was marked down-regulation of P27, Cyclin B, Cyclin D, Cyclin E, Cdk2 and Cdk4 compared to the RT control, but it was not statistically significant.

Combined IL-28/RT increases apoptosis of MiaPaCa-2 cells. The inhibition of MiaPaCa-2 cell growth can be a result of increased apoptosis caused by IL-28/RT. To address this possibility, we tested for the biological activity of the apoptotic marker, caspase-3, in MiaPaCa-2 cells after exposure to Il-28/RT. Compared to the MiaPaCa-2 cells that was treated with RT alone, the MiaPaCa-2 cells treated with IL-28/RT had significantly increased caspase-3 activity (Figure 3). This result indicates that IL-28/RT promotes apoptosis in MiaPaCa-2 cells, resulting in decreased survival.

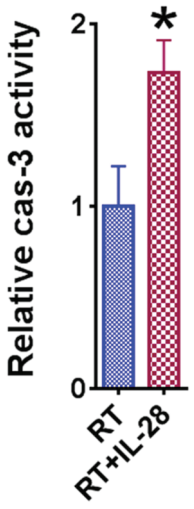

Figure 3. *Caspase-3 activity measured using the caspase-3/CPP32 colorimetric assay. Results are expressed as mean activity relative to controls (RT) and n=3. Error bars indicate standard error of the mean (SEM). *p<0.05 using Student's t-test.*

IL-28/RT alters expression of pro- and anti-apoptotic molecules in MiaPaCa-2 cells. To explore the potential molecular mechanism by which IL-28/RT induces apoptosis of MiaPaCa-2 cells, mRNA expression of major anti- and pro-apoptotic molecules was determined by RT-PCR after treatment with RT alone or IL-28/RT. We tested molecules that are essential factors of apoptosis: Fas, FasL, TRAILR1, TRAIL, Bax, FLIP, Bcl-2, and Survivin. We found that there was significant up-regulation of the pro-apoptotic molecule TRAILR1, and down-regulation of the anti-apoptotic molecule Survivin (Figure 4). Additionally, there was marked down-regulation in Bcl-2 and Bax, and marked up-regulation in Fas, but these were not significant (Figure 4). This pattern suggests there was increased apoptosis in MiaPaCa-2 cells upon exposure to IL-28/RT.

Discussion

Most pancreatic cancers are discovered at an advanced stage and, as such, often have metastasis beyond the pancreas that both complicates treatment and reduces overall survival (19, 20). Radiation therapy is a common component of intervention in treatment for metastasis and local cancer. However, pancreatic cancer is highly radioresistant and the majority of patients do not achieve optimal response to radiation therapy (21). As such, there is a critical need for potent radiosensitizers. We found that IL-28 with radiation significantly reduces the proliferation of pancreatic cancer cells. Furthermore, we determined that this combination induces changes of critical apoptotic molecules – P18, P21, TRAILR1, and Survivin.

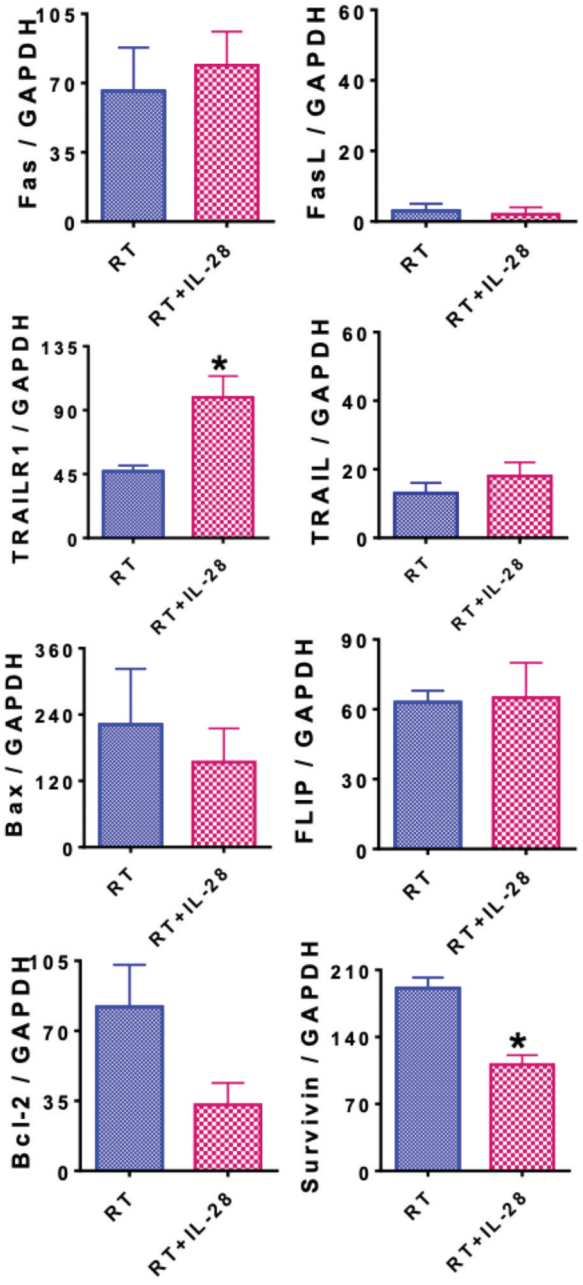

Figure 4. *Effect of IL-28/RT on expression levels of pro- and anti-apoptotic molecules in MiaPaCa-2 cells evaluated by RT-PCR. Results are expressed as the mean ratio of proliferative molecule densitometric units/GAPDH (n=3). Error bars indicate standard error of the mean (SEM). *p<0.05 using Student's t-test.*

To the best of our knowledge, this study is the first that provides insight into the anti-tumor effect of IL-28 on the MiaPaCa-2 pancreatic cancer cell line in combination with radiation therapy. Over the past years, our laboratory has been studying the radiosensitizing effects of various cytokines.

Similarly, to our findings of IL-28 on pancreatic cancer cells, we have found that IL-21 and IL-37 have radiosensitizing properties on different cancer cell lines (5, 9).

Uncontrolled cancer growth is often caused by a mutation in cellular apoptosis (5). One mechanism of inhibition of proliferation of MiaPaCa-2 can be attributed to the enhanced expression of P21, an anti-proliferative molecule. P21 is a key component that can suppress cell proliferation through p53 dependent G1 growth arrest (22). One unexpected finding in our study was the reduced expression of p18, an anti-proliferative molecule. We speculate that this counter-intuitive finding is due to the cancer cells' attempt to adapt and survive through the treatments, as was documented in previous studies (23, 24).

Additionally, our study found that IL-28/RT sensitizes MiaPaCa-2 to radiation *via* up-regulation of the pro-apoptotic molecule, TRAILR1, and down-regulation of the anti-apoptotic molecule, Survivin. TRAILR1, when bound by TRAIL, initiates a death-inducing signaling complex that ultimately leads to selective tumor cell apoptosis by recruitment of caspases such as caspase-3, which drive cell dismantling (25). The up-regulation of cascase-3 in concurrence with IL-28/RT further highlights this mechanism. Currently, TRAILR is a topic of interest in immunotherapy because it mediates apoptosis without toxicity against normal tissues (26). Prior studies from our lab have shown that IL-9 and the combination of IL-32 and kiwi extract up-regulate expression of TRAILR in melanoma cells (27). Further, pancreatic cancer is considered resistant to TRAIL-induced apoptosis and, therefore, the exact clinical utility of TRAIL-induced apoptosis is still being explored (28). The successful up-regulation of TRAILR1 expression with RT/IL-28 is a promising step towards targeted chemotherapy utilizing the TRAIL/TRAILR1 pathway.

Lastly, Survivin is an anti-apoptotic molecule that inhibits cell death. It is considered a molecular biomarker in cancer because it is highly expressed in most cancers (29), with one study detecting expression of Survivin in 81.95% of pancreatic cancer cell samples. Survivin functions by directly inhibiting the activities of caspase-3 and caspase-7 to block apoptosis (30). Thus, the decreased expression of Survivin is one explanation behind the sensitizing properties of IL-28.

This combination also greatly reduced cancer cell colony survival *in vitro*. MiaPaCa-2 survival and proliferation were significantly reduced from IL-28/RT compared to RT alone and control. Caspase-3 up-regulation in concurrence with IL-28/RT exposure further demonstrates this anti-tumor effect. The significant up-regulation of TRAILR1 and down-regulation of Survivin upon IL-28/RT therapy furthers this inference.

Limitations of our paper include the use of IL-28/RT in an *in vitro* experiment. Future experiments should occur in animal studies to determine pro- or anti-tumorigenic effects more systemically. Furthermore, only one cell line was studied in this experiment. Due to IL-28 being a prominent cytokine in the immunologic response, it is expected that similar studies should demonstrate similar results in other neoplasms.

Conclusion

In conclusion, our study successfully demonstrates the potential of IL-28 to be used as a radiation sensitizing agent for pancreatic cancer and future research should model this experiment on other cancer cell lines. Pancreatic cancer, as with many neoplasms, is a serious diagnosis that unfortunately has limited treatment options in modern medicine. Thus, sensitization of pancreatic cancer cells would allow clinicians to lower the amount of radiation required to treat radio-resistant pancreatic tumors, thus reducing the occurrence of harmful side effects.

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

Yujiang Fang designed the study. Yujiang Fang, Xuhui Chen, Hayden Y. Lee, Trien T. Tang, Chenglu Qin, Samuel A. Prissel, Christian J. Nelson, Huaping Xiao, and Qian Bai performed the experiments. Yujiang Fang, Xuhui Chen, Chenglu Qin, and Samuel A. Prissel, and Luke A. Smith analyzed the data. Yujiang Fang, Michael B. Nicholl, and Mark R. Wakefield interpreted the data. Hayden Y. Lee and Trien T. Tang wrote the draft and Yujiang Fang, Michael B. Nicholl, and Mark R. Wakefield revised the manuscript.

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