High TRAIL Death Receptor 4 and Decoy Receptor 2 Expression Correlates With Significant Cell Death in Pancreatic Ductal Adenocarcinoma Patients

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Objectives: The importance of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and TRAIL receptor expression in pancreatic carcinoma development is not known. To reveal the putative connection of TRAIL and TRAIL receptor expression profile to this process, we analyzed and compared the expression profile of TRAIL and its receptors in pancreatic tissues of both noncancer patients and patients with pancreatic ductal adenocarcinoma (PDAC).

Methods: Thirty-one noncancer patients and 34 PDAC patients were included in the study. TRAIL and TRAIL receptor expression profiles were determined by immunohistochemistry. Annexin V binding revealed the apoptotic index in pancreas. Lastly, the tumor grade, tumor stage, tumor diameter, perineural invasion, and number of lymph node metastasis were used for comparison purposes.

Results: TRAIL decoy receptor 2 (DcR2) and death receptor 4 expression were up-regulated in PDAC patients compared with noncancer patients, and the ductal cells of PDAC patients displayed significant levels of apoptosis. In addition, acinar cells from PDAC patients had higher DcR2 expression but lower death receptor 4 expression. Increased DcR2 expression was also observed in Langerhans islets of PDAC patients.

Conclusions: Differential alteration of TRAIL and TRAIL receptor expression profiles in PDAC patients suggest that the TRAIL/TRAIL receptor system may play a pivotal role during pancreatic carcinoma development.

Key Words: TRAIL, pancreas, ductal adenocarcinoma, cell death

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P ancreatic cancer (PC) is the fourth leading cause of cancerrelated death, with an overall 5-year survival rate of 4% after diagnosis.¹ Of 31,860 newly diagnosed PCs, 31,270 patients died in 2004 as reported by the American Cancer Society. Pancreatic ductal adenocarcinoma (PDAC) is a highly malignant and invasive form of PC,² as the median survival rate of PDAC patients is less than 6 months.³ At the time of

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diagnosis, ~40% of patients with PC have metastatic disease, 40% to 50% have locally advanced stage disease that is not amenable to surgery, and only ~10% of patients can go through a potentially curative resection.⁴ Unfortunately, the result of surgery alone is relatively poor, with an ~80% rate of local or distant recurrence, and the 5-year survival rate for cases involving total resection is only 10% to 24%.^{5–8}

Because of the high mortality rate in PDAC, novel treatment modalities, such as gene therapy, are being explored to develop effective alternative treatments for PDAC patients. One of the therapeutic genes, which has currently been evaluated in the context of gene therapy, is tumor necrosis factor-related apoptosis-inducing ligand (TRAIL).9 TRAIL is a type II membrane protein that can bind to 5 different receptors: TRAIL-R1 (DR4), TRAIL-R2 (DR5), TRAIL-R3 (DcR1), TRAIL-R4 (DcR2), and osteoprotegrin.¹⁰ DR4 and DR5 are the death receptors that signal for apoptosis, whereas DcR1, DcR2, and osteoprotegrin are considered antagonistic because they are unable to induce such signaling because of the lack of intracellular death domain or are secreted molecules.11 In comparison to the other death-inducing members of the tumor necrosis factor family (Fas ligand and tumor necrosis factor), TRAIL has discrete apoptosis-inducing properties on cancer cells. In particular, TRAIL is a potent inducer of tumor cell apoptosis¹² but is nontoxic to normal cells and tissues.^{13,14} Interestingly, an adenovirus vector encoding the TRAIL cDNA (Ad-TRAIL) efficiently killed pancreatic tumors in vitro and in vivo.¹⁵ Furthermore, systemic administration of Ad-TRAIL suppressed pancreatic tumor growth in the liver.¹⁶ Despite these encouraging results, the mechanism(s) that regulate the TRAILmediated signaling cascade is not well understood,17,18 and there is significant effort investigating why more than 50% of human tumors are TRAIL resistant.¹⁹ For example, analysis of PDAC cell lines revealed variable degrees of TRAIL sensitivity due to TRAIL decoy receptor gene expression.²⁰

Resistance to TRAIL-induced apoptosis can occur at various levels in the TRAIL signaling cascade. High DcR2 expression was recently correlated with TRAIL resistance in breast, prostate, and lung cancer cell lines,^{21–23} and siRNA strategy targeting DcR2 sensitized both lung and prostate cancer cells to TRAIL.^{23,24} Intriguingly, PC cells differentially express DcR1 and DcR2,²⁵ and DcR2 overexpression mediates TRAIL resistance in PC cells.²⁶ In accordance with this, the lack of TRAIL death receptor (DR4 or DR5) gene expression was also implicated in TRAIL resistance in PC cell lines.²⁷ Thus, TRAIL and TRAIL receptor expression profiles in PC patients may predict the feasibility of using TRAIL gene therapy as a treatment option.

In addition, the lack of early detection systems and inherent resistance of PDAC to all known conventional treatment modalities have contributed to the high mortality rate observed in PDAC.²⁸ Because the overexpression of transforming growth

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factor β type II receptor in PDAC patients has been associated with decreased survival,²⁹ the evaluation of novel markers was suggested for an early detection and follow-up of PC patients.³⁰ One of the potential markers useful for the follow-up of PDAC patients may be TRAIL.³¹ However, it is unclear how the TRAIL/TRAIL receptor system contributes to carcinogenesis. Benign and malignant prostate cancer cells differentially display TRAIL and its receptors, and this profile was connected to prostate carcinogenesis.³² In addition, high DcR2 expression is correlated with high Gleason scores, prostate-specific antigen recurrence, and decreased survival in patients with prostate carcinoma.³³ Lastly, DR4 expression positively correlated with tumor grade in breast cancer patients with invasive ductal carcinoma.³⁴ These studies suggest that the expression of TRAIL and its receptor in non-PDAC versus PDAC patients can provide useful information on the development of PDAC. Ultimately, we believe that understanding the expression profile of TRAIL and the TRAIL receptors in PDAC patients may elucidate a potential mechanism of pancreatic carcinoma.

MATERIALS AND METHODS

Immunohistochemistry Procedure Using Antibodies Developed Against TRAIL/TRAIL Receptors on Pancreas

Hematoxylin counterstaining was performed on all pancreatic tissue sections as described previously.^{23,32,34} The following primary antibodies (Alexis Biochemicals, Lausen, Switzerland) were used at 1:300 dilution for the staining of pancreatic tissues: anti-human TRAIL (III6F; ALX-804-326-C100), anti-human DR4 (HS101; ALX-804-297A-C100), anti-human DR5 (ALX-210-743-C200), anti-human DcR1 (ALX-210-744-C200), and anti-human DcR2 (HS402; ALX-804-299A-C100). Pancreatic tissue samples that were stained only with the secondary antibody were used as negative controls.

Quantitative Assessment of TRAIL and TRAIL Death-Decoy Receptor Expressions for Immunohistochemical Scoring

Tissue sections were analyzed by a single pathologist (O.E.) with no prior knowledge of the patient status or antibodies used. The calculation of the final immunohistochemical staining scores in pancreatic tissues included both intensity and marker distribution (percentage of the positively stained epithelial cells). The intensity of the pancreatic tissue staining was assessed as follows: 0, negative; 1, weak; 2, moderate; and 3, strong. Moreover, marker distribution was calculated as 0, less than 10%; 1, 10% to 40%; 2, 40% to 70%; and 3, more than 70% of the epithelial cells stained on the sections. Summing the scores of both the intensity and the marker distribution for a given patient resulted in the final immunostaining score.

Detection of Apoptotic Cells With Annexin V

Paraffin-embedded tissues were sectioned at 4- μ m thickness. Antigen retrieval was accomplished by boiling samples in a solution containing 0.01 M citrate buffer for 20 minutes after the deparaffinization and dehydration processes. The samples were then treated with proteinase K for 10 minutes. An annexin V fluorescent microscopy kit (BD Pharmingen, San Diego, Calif) was used to identify apoptotic cells in the pancreas. Pancreas sections were washed with 1× phosphate-buffered saline, followed by 1× annexin V–binding buffer (BD Pharmingen). Pancreatic tissue sections were then treated with annexin



FIGURE 1. Immunohistochemical staining of TRAIL and TRAIL receptors in noncancer patients (n = 31) versus patients with PDAC (n = 34). Representative images are provided from pancreatic ductal region of noncancer patients (upper panels), normal ductal region of cancer patients (middle panels), and from PDAC tissues (lower panels). TRAIL and TRAIL receptor subtypes are listed above each image, and each image represents a single patient.

V-fluorescein isothiocyanate (FITC) diluted 1:10 in 1× annexin V-binding buffer for 15 minutes at room temperature. Annexin V-FITC-stained cells were analyzed under fluorescent microscopy after washing samples in annexin V-binding buffer. To determine the extent of apoptosis in each section, positive and negative cells were counted in randomly selected highpower fields of acinar, ductal, or islet cells (area of each field is ~0.06 mm²). The apoptotic index was calculated as the percentage of annexin V-positive cells based on the ratio of annexin V-stained cells to the total number cells counted.

Statistical Analysis

Statistical analyses were performed using SPSS 13.0 software for Windows (SPSS Inc, Chicago, Ill). Statistical significance was considered at 5% probability level (P < 0.05). The SEM is displayed as error bars for all data points in all of the figures.

RESULTS

Clinical Assessment of Patients With PDAC

Pancreatic tissue samples from 34 patients with pancreatic ductal carcinoma and 31 patients without PC (as a control group) were evaluated. The median age of PC patients was 55 years, ranging from 1 to 80 years, whereas the median age of patients without the PC was 54 years, ranging from 36 to 74 years. All of the patients were clinically staged according to the American Joint Committee on Cancer guidelines. Based on this staging system, 3 cases (8.8%) were T1, 10 cases (29.4%) were T2, 11 cases (32.4%) were T3, and 10 cases (29.4%) were T4. Thirteen patients (38%) had well-differentiated tumors, whereas 17 (50%) had moderate levels of differentiation. Only 4 cases (12%) had poorly differentiated pancreatic tumors. Perineural invasion was observed in 13 patients (38%), and 8 (24%) of the PC patients displayed lymph node metastasis. Whipple operation (R0/R1) was performed in 18 patients. Biopsies (R2) were taken from 16 patients. Both definitive and adjuvant external radiotherapy at a median dose of 50.4 Gy in 28 fractions was delivered to the primary region and to the lymphatics. Twentynine patients concurrently received 5-fluorouracil-based che-



FIGURE 2. Quantitative analysis of the immunohistochemical ductal staining of non-PDAC versus PDAC patients. Immunohistochemical scoring (mean \pm SEM) was performed as described in the Materials and Methods using the indicated antibodies. Asterisk indicates statistically significant differences among the 3 groups.



FIGURE 3. Acinar staining patterns of TRAIL and TRAIL receptors in pancreatic tissues of non-PDAC (upper panels) versus PDAC patients (lower panels). A, Representative images of immunohistochemical staining, where each image is taken from a single patient. B, Quantitative analyses of the immunohistochemical staining (mean \pm SEM) of pancreata dissected from non-PDAC patients are displayed in open bars, whereas those for pancreata of PDAC patients are shown in solid bars. Asterisk indicates statistically significant differences between the 2 groups.

motherapy. Neoadjuvant treatment was used only in 11 of these patients.

High DR4 and DcR2 Expressions Were Detected in Patients With Pancreatic Adenocarcinoma

Patients were divided into 2 groups based on the presence or absence of tumor in the pancreas (PDAC). In addition, the PDAC patients were further subdivided into 2 groups based on immunohistochemical staining of the tumor itself or the surrounding nontumoral pancreatic ductal tissue. Representative images of pancreatic ductal staining from different patient groups are shown in Figure 1. Whereas TRAIL, DcR1, and DcR2 expressions were clearly detectable in the pancreatic ductal tissue of non-PC patients and the nontumoral ductal region of the PC patients, DR4 and DR5 expressions were not readily detectable in these cases. In contrast, tumor tissues of PDAC patients expressed TRAIL and all 4 TRAIL receptors. Furthermore, TRAIL was the highest marker expressed in PDAC tissue sections. Kolmogorov-Smirnov test (n = 99) was used to determine whether the patient groups were normally distributed. Because a Gaussian distribution was not detected, the statistical difference among the groups was determined using the Kruskal-Wallis test. The groups were then paired for comparison using the Mann-Whitney U test. Quantitative analysis of the immunohistochemical staining suggested that both DR4 and DcR2 expressions were up-regulated in PDAC patients compared with nonneoplastic pancreatic ductal tissues of the same patients or noncancer patients (Fig. 2). It is interesting to note that nonneoplastic pancreatic ductal tissues of cancer patients displayed intermediate levels of DR4 and DcR2 expressions compared with pancreatic ductal tissues of non-cancer patients or PDAC sections.

Patients With PDAC Displayed Increased DcR2 Expression in the Acinar Cells Compared With Nontumor Patients

Acinar cell immunohistochemical staining for TRAIL and the TRAIL receptors were also compared between patients with or without PDAC. As shown in Figure 3A, the death and decoy TRAIL receptors were expressed in the acinar cells of the pancreas in patients with or without PDAC. The quantitative expression profiles of the each molecule are shown in Figure 3B. First, the normality of the groups was tested by Shapiro-Wilk method. Because neither group displayed a Gaussian distribution, the Mann-Whitney U test was used to determine the statistical significance between the 2 groups. Whereas lower DR4 expression and higher DcR2 expression were detected in the acinar cells of PDAC patients compared with noncancer patients, TRAIL was expressed the highest in acinar cells of patients with or without PDAC.

High DcR2 Expression Was Observed in Langerhans Islets of the Patients With Pancreatic Adenocarcinoma Versus Noncancer Patients

We next measured TRAIL and TRAIL receptors expression on the Langerhans islets. Although DR4 and DR5 were not





FIGURE 4. Langerhans islet staining of TRAIL and TRAIL receptors in pancreatic tissues of non-PDAC (upper panels) versus PDAC patients (lower panels). A, Representative images of immunohistochemical staining, where each image is taken from a single patient. B, Quantitative analysis of immunohistochemical staining (mean \pm SEM), with open bars representing non-PDAC patients and solid bars representing patients with PDAC. Asterisk indicates a significant difference between the 2 groups of patients.

| TABLE 1. Correlation Between TRAIL and TRAIL Receptor | |
|---|---|
| Expression in PDAC Patients as Determined by Spearman | ρ |
| Correlation Test | |

| Spearman <i>ρ</i> | | | | | | | |
|-------------------|-------------------------|-------------|--------|--------|-------|--------|--|
| Correla | tions | DR4 | DR5 | DcR1 | DcR2 | TRAIL | |
| DR4 | Correlation coefficient | 1.000 t | -0.154 | -0.130 | 0.065 | 0.069 | |
| | P (2-tailed) | | 0.384 | 0.465 | 0.714 | 0.698 | |
| | n | 34 | 34 | 34 | 34 | 34 | |
| DR5 | Correlation coefficient | -0.154 t | 1.000 | 0.311 | 0.284 | 0.228 | |
| | P (2-tailed) | 0.384 | | 0.074 | 0.103 | 0.194 | |
| | n | 34 | 34 | 34 | 34 | 34 | |
| DcR1 | Correlation coefficient | -0.130 t | 0.311 | 1.000 | 0.170 | 0.427* | |
| | P (2-tailed) | 0.465 | 0.074 | — | 0.335 | 0.012 | |
| | n | 34 | 34 | 34 | 34 | 34 | |
| DcR2 | Correlation coefficient | 0.065 t | 0.284 | 0.170 | 1.000 | 0.090 | |
| | P (2-tailed) | 0.714 | 0.103 | 0.335 | _ | 0.613 | |
| | n | 34 | 34 | 34 | 34 | 34 | |
| TRAIL | Correlation coefficient | 0.069 t | 0.228 | 0.427* | 0.090 | 1.000 | |
| | P (2-tailed) | 0.698 | 0.194 | 0.012 | 0.613 | _ | |
| | n | 34 | 34 | 34 | 34 | 34 | |
| | | - | | | | | |

*Correlation is significant at the 0.05 level (2-tailed).

clearly detectable because of low expression, both DcR1 and DcR2, as well as TRAIL, were readily detectable in the pancreatic islets of both patient groups (PC patients vs non-PC patients; Fig. 4A). In addition, TRAIL was expressed the highest compared with the TRAIL receptors in Langerhans islets. Because neither of the patient groups exhibited a Gaussian distribution as tested by the Shapiro-Wilk method, the Mann-Whitney U test was performed to determine statistical significance between the 2 groups. Patients with PDAC expressed statistically higher amounts of DcR2 on Langerhans islets compared with patients without the tumor.

DcR1 and TRAIL Expression Were Positively Correlated in Patients With Pancreatic Adenocarcinoma

The Spearman ρ correlation test was next used to test any correlation among the TRAIL markers in PDAC patients. Table 1 shows that only DcR1 and TRAIL expressions were positively correlated in these patients. No such correlation was detected when tumor grade, tumor stage, tumor diameter, perineural invasion, number of lymph node metastasis were taken into account (data not shown).

PDAC Tissues Showed Increased Apoptosis Compared With Pancreata of Noncancer Patients

The presence of apoptotic cells in the pancreas and their correlation to TRAIL and TRAIL receptor expression were analyzed using FITC-conjugated annexin V. Although the fluorescent microscopic images in Figure 5 display annexin V–FITC–stained cells, a quantitative assessment of cell death is provided in Figure 6. Among the tissue sections analyzed, both nontumoral and tumoral ductal region of pancreas in PDAC patients exhibited increased apoptosis compared with pancreata of noncancer patients. However, no correlation was detected between TRAIL marker expression and the amount of cell death



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FIGURE 5. Assess of apoptosis in the pancreas by annexin V-FITC binding. Quantification of apoptotic cells was performed as described in Materials and Methods. A, Representative images (original magnification ×200) of acinar (left), ductal (middle), and islet cells (right). Normal pancreas tissue sections are in the upper row, whereas nontumoral regions of pancreatic tissue dissected from PC patients are in the lower row. B, Annexin V–FITC staining of 3 different PDAC cases (original magnification \times 200). Images in the lower panels are taken at high-power magnification (original magnification \times 400) of the same fields.

observed in pancreatic ductal cells of PDAC patients (data not shown). Conversely, islet, but not ductal or acinar, cell death correlated with high TRAIL expression as revealed by Spearman ρ correlation test in PDAC patients (Table 2). Annexin V-binding assay results were also confirmed using TUNEL assay (data not shown).

DISCUSSION

Because PDAC is resistant to conventional treatment methods and exhibits high mortality rates, novel treatment modalities are needed to improve survival rates of PDAC patients. Furthermore, there is also a necessity to discover new PC tumor markers for both diagnostic and prognostic purposes. Although adenovirus delivery of TRAIL effectively kills pancreatic tumor cell lines in vitro and in vivo,¹⁵ high TRAIL decoy receptor expression²⁰ and TRAIL-mediated nuclear factor κ B activity³⁵ were implicated for TRAIL resistance in PDAC. Thus, it is important to know the in vivo expression profiles of TRAIL and the TRAIL receptors in patients with PDAC. Previously, the expression of TRAIL and the 4 TRAIL receptors were determined by reverse transcriptase-polymerase chain reaction in 17 cases of PDAC and 5 cases of normal pancreatic



FIGURE 6. Quantitative analysis of apoptotic index. Apoptotic scores (mean ± SEM) of pancreas sections of noncancer patients (open bars), nontumoral regions of PC patients (shadowed bar), and PDAC tissues (solid bars) were determined. *P < 0.05.

tissues.36 Both normal pancreata and pancreata of PDAC patients displayed varying degrees of TRAIL and TRAIL receptor expression. Although reverse transcriptase-polymerase chain reaction is a useful method to detect the presence or absence of gene expression, mRNA expression does not necessarily correlate with the protein expression in the cell or on the cell surface. The expressions of TRAIL, DR4, and DR5 were analyzed in another study involving 10 non-PC and 11 PC patients.37 It was found that despite the expression of TRAIL, DR4, and DR5, the PC cells displayed low sensitivity to TRAILmediated apoptosis compared with Jurkat T-lymphoma cells. However, this study excluded the analysis of TRAIL decoy receptor gene expression.

In the data described herein, immunohistochemistry analyses were used to determine the tissue distribution pattern

| TABLE 2. | Correlation of Apoptotic Islet Cells With | TRAIL |
|-----------|---|-------|
| and TRAIL | Receptor Profiles in Pancreas | |

| ng | Islets |
|-------------------------|--|
| Correlation coefficient | 0.228 |
| P (2-tailed) | 0.194 |
| n | 34 |
| Correlation coefficient | 0.283 |
| P (2-tailed) | 0.105 |
| n | 34 |
| Correlation coefficient | 0.317 |
| P (2-tailed) | 0.068 |
| n | 34 |
| Correlation coefficient | 0.139 |
| P (2-tailed) | 0.434 |
| n | 34 |
| Correlation coefficient | 0.389* |
| P (2-tailed) | 0.023 |
| n | 34 |
| | Correlation coefficient P (2-tailed) n Correlation coefficient P (2-tailed) n Correlation coefficient P (2-tailed) n Correlation coefficient P (2-tailed) n Correlation coefficient P (2-tailed) n |

and expression of TRAIL and the 4 TRAIL receptors as a complete set in both non-PDAC (n = 31) and PDAC patients (n = 34). Our results indicate that TRAIL expression was highest on average compared with the expression profiles of TRAIL death and decoy receptors particularly in PDAC tissues. As recently suggested, high TRAIL expression may be important for the protection of tumor cells from attacking inflammatory cells.^{20,37} In accordance with this observation, TRAIL enhanced the metastatic spread of orthotopically transplanted human PDAC cells in severe combined immunodeficient mice.³⁸ Thus, high TRAIL expression on cancer cells might be beneficial for metastasis considering immuneprotection and invasion scenarios. In addition, high DcR2 expression in PDAC tissues compared with nonneoplastic ductal cells may also allow these cells to escape from TRAILmediated apoptosis. Although the functional consequence of increased DR4 expression in PDAC tissues is currently not known, PDAC cells displayed resistance to TRAIL-mediated apoptosis despite high levels of death receptor expression.³⁷

In addition, acinar cells of PDAC patients expressed lower DR4, but higher DcR2 expression, suggesting that not only PDAC cells but also acinar cells of PDAC patients have developed a mechanism to escape apoptosis compared with patients without cancer. Apart from the exocrine constituent, Langerhans islets are the discrete units of endocrine compartment of the pancreas. The failure of pancreatic beta cell function due to autoimmune destruction mediated by islet-reactive T cells results in type 1 diabetes. The expression profiles of TRAIL and the TRAIL receptors were also analyzed in Langerhans islets of non-PDAC versus PDAC patients. The Langerhans islets from both non-PDAC and PDAC patients expressed considerable TRAIL, DcR1, and DcR2, but only the low expressions of DR4 and DR5 were detected in both cases. Interestingly, increased TRAIL expression was observed in the infiltrating immune cells of pancreatic islets in patients with type 1 diabetes.³⁹ Thus, under normal circumstances, Langerhans islets are expected to be protected from the immunemediated attacks through TRAIL expression and from death ligand-mediated apoptosis by way of decoy receptor expression.⁴⁰ Because Langerhans islets of PDAC patients exhibited higher DcR2 expression compared with noncancer patients, it would be interesting to see if these patients are more resistant to developing type 1 diabetes compared with noncancer patients.

Spearman ρ correlation test suggested the existence of a positive correlation between TRAIL and DcR1 expression in PDAC patients. Although increasing the level of TRAIL decoy receptor expression might be necessary for protection from T cell-mediated attacks, TRAIL overexpression might endanger tumor cell survival because it would activate apoptotic pathways. One of the ways to counteract the action of TRAIL is to up-regulate decoy receptor expression on surface. DcR1 expression blocks TRAIL-mediated apoptosis by acting as a decoy receptor.⁴¹ Thus, PDAC cells might be protected from the side effects of TRAIL overexpression through up-regulation of TRAIL decoy receptor expression.

Annexin V-binding indicated that pancreatic ductal tissues of PDAC patients exhibited increased apoptosis compared with pancreata of noncancer patients. It is interesting to note that PDAC tissues also displayed increased DR4 expression. Although these cells also had increased DcR2 expression, the up-regulation of DcR2 was not sufficient to protect PDAC cells from apoptosis. In addition, although there was lower DR4 expression and higher DcR2 expression seen in acinar cells of PDAC patients, there was no difference in the apoptotic index detected between the 2 groups. Similarly, although there was higher DcR2 expression detected in islet cells of PDAC patients compared with noncancer patients, annexin V–FITC staining did not indicate any difference in apoptosis between the 2 patient groups. Islets of PDAC patients exhibited less apoptosis compared with acinar cells of the same patient group. This can be explained by the DR4 expressed on acinar cells of PDAC patients, which was expressed higher than that seen on islets. Nevertheless, similar to the observation reported before in noncancer patients,³¹ TRAIL expression displayed a positive correlation with increased cell death in PDAC patients.

In conclusion, the TRAIL and TRAIL receptor expression profile may play critical roles during pancreatic carcinoma development by way of modulating apoptotic cell death.

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