Original paper

Survivin and caspase-3 and PanIN. Disorders of apoptosis in the process of pancreatic cancer formation

Surwiwina i kaspaza 3 a PanIN. Zaburzenia apoptozy w procesie powstawania raka trzustki

Konrad Zaręba[1], Justyna Dorf[2], Kerianne Cummings[3], Anna Pryczynicz[4], Katarzyna Guzińska-Ustymowicz[4], Bogusław Kędra[1]

[1]2nd Clinical Department of General, Gastroenterological and Oncological Surgery, Medical University of Bialystok, Bialystok, Poland
[2]Department of Clinical Laboratory Diagnostics, Medical University of Bialystok, Bialystok, Poland
[3]Students' Scientific Association, 2nd Clinical Department of General, Gastroenterological and Oncological Surgery, Medical University of Bialystok, Bialystok, Poland
[4]Department of General Pathomorphology, Medical University of Bialystok, Bialystok, Poland

Medical Studies/Studia Medyczne 2024; 40 (1): 1–7
DOI: https://doi.org/10.5114/ms.2024.137585

Key words: caspase-3, PanIN, apoptosis, survivin.

Słowa kluczowe: kaspaza 3, PanIN, apoptoza, surwiwina.

Abstract

Introduction: It is believed that pancreatic intraepithelial neoplasia is an important element of pancreatic carcinogenesis. Apoptosis is the process of programmed cell death. Survivin is one of the proteins that inhibit apoptosis. Caspase-3 is a cysteine protease, and plays important roles in the process of apoptosis.
Aim of the research: The authors focus on analyzing the expression of survivin and caspase-3 in unchanged tissue and tissue from PanIN lesions. This study may help to better understand the cause-and-effect chain from low-grade intraepithelial neoplasia to high-grade neoplasia and invasive cancer.
Material and methods: The study used tissue material obtained from 70 patients operated on at the 2nd Department of General, Gastroenterological and Oncological Surgery at the Medical University of Bialystok due to pancreatic diseases: adenocarcinoma (38 patients), chronic pancreatitis (23 patients), pancreatic cysts (9 patients). A total of 239 tissue samples were isolated for clinical examination.
Results: There were statistically significant differences in survivin expression by sex ($p < 0.05$) and age ($p < 0.05$). The level of survivin expression was higher in male patients and patients over 60. There were statistically significant differences between the expression levels of survivin as well as caspase-3 depending on the degree of PanIN [PanIN 1A vs PanIN 1b survivin 15% vs. 38.8% ($p < 0.05$), and caspase-3 17%; vs. 26.9% ($p < 0.05$). PanIN 2 vs. PaIN3 survivin 62.4% vs. 85.7% ($p < 0.05$), caspase-3 36.1% vs. 54.3% ($p < 0.05$)].
Conclusions: The expression level of survivin and caspase-3 is inextricably linked with the progression of pancreatic intraepithelial neoplasia. The more advanced neoplasia is, the higher is the expression level.

Streszczenie

Wprowadzenie: Apoptozą nazywamy proces zaprogramowanej śmierci komórki. W procesie tym ważną rolę odgrywają m.in. takie białka, jak surwiwina i kaspaza 3. Zaburzenia procesu apoptozy prowadzą do występowania procesu nowotworzenia. Jedną ze zmian przednowotworowych, jakie obserwujemy u chorych z rakiem trzustki, są zmiany o charakterze PanIn.
Cel pracy: Ocena ekspresji surwiwiny i kaspazy 3 w niezmienionej tkance trzustki oraz w ogniskach PanIN – zmianach przednowotworowych. Badanie ma na celu zrozumienie ciągu przyczynowo-skutkowego prowadzącego od śródnabłonkowej neoplazji małego stopnia, przez neoplazję dużego stopnia do raka inwazyjnego.
Materiał i metody: W badaniu wykorzystano materiał tkankowy uzyskany od 70 chorych operowanych w II Klinice Chirurgii Ogólnej, Gastroenterologicznej i Onkologicznej Uniwersytetu Medycznego w Białymstoku z powodu następujących chorób trzustki: rak (38 chorych), przewlekłe zapalenie trzustki (23 chorych), torbiele trzustki (9 chorych). Z materiału pooperacyjnego wyizolowano do badania klinicznego łącznie 239 próbek tkankowych: 35 – niezmieniona tkanka, 65 – PanIN 1a, 67 – PanIN 1b, 51 – PanIN 2, 21 – PanIN 3.
Wyniki: Stwierdzono statystycznie istotne różnice w ekspresji surwiwiny w zależności od płci i wieku ($p < 0,05$). Poziom surwiwiny był istotnie wyższy u mężczyzn oraz u chorych powyżej 60. roku życia. Wykazano statystycznie istotne różnice w ekspresji surwiwiny i kaspazy 3 w zależności od nasilenia zmian PanIN [PanIN 1A *vs* PanIN 1b surwiwina 15% *vs* 38,8% ($p < 0,05$; kaspaza 3 17%; *vs* 26,9% ($p < 0,05$). PanIN 2 *vs* PaIN3 surwiwina 62,4% *vs* 85,7% ($p < 0,05$), kaspaza 3 36,1% *vs* 54,3% ($p < 0,05$)].
Wnioski: Poziom ekspresji surwiwiny i kaspazy 3 jest nierozerwalnie związany z zaawansowaniem PanIN. Im bardziej zaawanowana jest neoplazja, tym poziom ekspresji jest wyższy, co skutkuje szybszym rozwojem raka inwazyjnego trzustki.

Introduction

Despite continuous advancements in the diagnosis and treatment of gastrointestinal neoplasms, these conditions remain challenging in routine medical practice. At present, it is noted that globally, pancreatic cancer is the 7th leading cause of neoplastic-related mortality.

In the year 2018, a total of 458,918 pancreatic neoplasms were diagnosed globally; subsequently, there were 432,242 recorded deaths related to pancreatic cancer [1, 2]. Among the aforementioned cases, adenocarcinoma is the prominent lesion, totaling 80–85% of all pancreatic neoplasms [1, 3]. Additionally, 10–20% of patients have a resectable neoplastic pancreatic lesion at the time of diagnosis with an estimated 20% 5-year survival rate. Considering all pancreatic cancer patients, the 5-year survival probability is less than 5% [1, 4]. To further emphasize the complexity of pancreatic cancer, 2 years of survival is achieved in approximately 8% of patients [2, 5]. The average survival time in a patient diagnosed with pancreatic cancer is an estimated 6 months [1, 2].

Pancreatic cancer risk factors include lifestyle habits, blood group, and genetic factors. Lifestyle habits corresponding to the development of pancreatic cancer include smoking, being overweight or obese, regular consumption of large amounts of alcohol, and excessive consumption of red meat and saturated fat [6–8]. A significantly higher rate of pancreatic cancer was also observed in patients with blood group A [1, 6, 8]. Among the genetic factors, the following syndromes have been associated with pancreatic lesions [1, 6–8]: 1) hereditary breast and ovarian cancer, 2) hereditary non-polyposis colorectal cancer – HNPCC, 3) Peutz-Jeghers syndrome – PJS, 4) familial adenomatous polyposis – FAP, 5) familial pancreatic cancer – FPC, 6) hereditary pancreatitis.

The importance of precancerous pancreatic lesions, such as intraepithelial pancreatic neoplasia (PanIN), intraductal papillary mucous neoplasms (IPMN), and cystic mucinous neoplasms, is raised in the literature [9–14]. PanIN, i.e. intraepithelial pancreatic neoplasia, is an asymptomatic lesion ≤ 5 mm, flat or papillary, which originates from small pancreatic ducts. It is divided into three subtypes [12–14]:

1. Low-grade neoplasia, i.e. PanIN-1, in which slight cytological and architectural atypia is observed. Within PanIN-1, we distinguish PanIN-1A, described as a flat lesion, and PanIN-1B, described as a papillary lesion.
2. Moderate neoplasia, i.e. PanIN-2, illustrates architectural and cytological atypia which is moderate for the loss of polarity of the cell nucleus, pseudo-ordering, crowding of cell nuclei, pleomorphism of the size of cell nuclei, and hyperchromatic cell nuclei.
3. High-grade neoplasia, i.e. PanIN-3, can be characterized by the architecture and structure of cells, which are subject to increased modification, among other features. Mitotic figures and even abnormal mitoses may be visible.

It is believed that pancreatic intraepithelial neoplasia is an important element in the process of carcinogenesis and leads to the emergence and establishment of genetic disorders within cells, which results in the progression of neoplasia from low to high, and then into invasive cancer [9, 10, 12–14].

Apoptosis is the process of programmed cell death. Programmed cell death can be accomplished via the intrinsic pathway or extrinsic pathway. The intrinsic apoptosis pathway can be induced by cell damage caused by external factors such as UV light, ionizing radiation, and chemicals [15, 16]. It is regulated by several initiatory and inhibitory proteins (BCL-2, BCL-XL, BAX/BAK). In the case of the extrinsic pathway, activation of ligand binding to a specific cell receptor in turn causes activation of caspases that participate in programmed cell death [15].

The extrinsic pathway, which is also referred to as the death receptor pathway, allows for apoptosis of cells via cytotoxic CD8+ T cells. Preceding the actual apoptosis, the extrinsic pathway is initiated via binding of Fas-L to Fas (CD95) while TNF-α simultaneously binds to the TNF receptor on cancer cells. This activates granzyme B and perforin release from cytotoxic CD8+ T cells [15, 16].

Survivin is one of the proteins that inhibit apoptosis. It was discovered in 1997 by Ambrosini *et al.* [17] in B-cell lymphoma. Survivin, an antiapoptotic protein, was discovered in 1997 by Ambrosini *et al.* [17] in B-cell lymphoma. It has as molecular weight of 16.5 kDa and the gene responsible for its encoding is located on the 17q25 chromosome.

Survivin inhibits caspase activation, specifically caspase-3, -7, and -9, via direct and indirect mechanisms.

Caspase-3 is inhibited indirectly while caspase-7 and caspase-9 are directly inhibited. Caspase-3 is a cysteine protease; in the family of these proteases, we distinguish both initiator and executioner caspases. They are all synthesized in the form of an inactive zymogen. Initiation of apoptosis begins with the activation of initiation caspases and is followed by executioner caspases activation. Caspase-3 is classified as an executioner caspase and is responsible for one of the most important roles in the process of apoptosis. Survivin inhibition of apoptosis occurs at the G1/S and G2/M cell cycle checkpoints [18–20].

Aim of the research

In the aforementioned work, the authors focus on analyzing the expression of survivin and caspase-3 in tissue from PanIN lesions. Concurrently, we wanted to compare how the progression of the precancerous stage, PanIN, affects apoptotic disorders and transitions to invasive carcinoma.

Material and methods

The study used tissue material obtained from 70 patients operated on at the 2nd Department of General, Gastroenterological and Oncological Surgery Medical University of Bialystok due to pancreatic diseases such as adenocarcinoma (38 patients), chronic pancreatitis (23 patients) and pancreatic cysts (9 patients). There were 35 women and 35 men in the study group. The patients were divided into 2 groups according to their age: group I consisted of patients under 60, $n = 33$ (47.2%), while group II consisted of patients over 60 years of age, $n = 37$ (52.8%). The primary lesions for which the patients were operated on were located as follows: 33 cases in the head of the pancreas, 5 cases in the body of the pancreas, 20 cases in the tail of the pancreas, and 12 cases in the body and tail of the pancreas. The basic characteristics of the study group are presented in Table 1. A total of 239 tissue samples were isolated for clinical examination from the postoperative material: 35 samples from unchanged tissue, 65 samples from PanIN-1A lesions, 67 from PanIN-1B neoplasia, 51 from PanIN-2, while PanIN-3 was found in 21 samples. The above data are presented in Table 2.

The study was performed in conformity with the Declaration of Helsinki for Human Experimentation and received approval of the Local Bioethics Committee of the Medical University of Bialystok (No. R-I-002/139/2014).

Table 1. Characteristics of the study group

Clinicopathological features	Frequency *n* (%)
Sex:	
Male	35 (50%)
Female	35 (50%)
Age:	
< 60 years	33 (47.2%)
≥ 60 years	37 (52.8%)
Diagnosis:	
Pancreatitis	23 (32.9%)
Pancreatic ductal adenocarcinoma	38 (54.3%)
Pancreatic cysts	9 (12.8%)
Location:	
Head	33 (47.1%)
Body	5 (7.1%)
Tail	20 (28.6%)
Body and tail	12 (17.2%)

Histopathological examination and identification of ductal lesions

In brief, formalin-fixed and paraffin-embedded tissue specimens were cut on a microtome into 5-µm sections and stained with hematoxylin-eosin (H&E stain). Routine histopathological analysis included diagnosis of primary disease, but also the presence and stage of pancreatic intraepithelial neoplasia. All slides were reviewed by two independent pathologists for the presence and grade of PanIN lesions in accordance with the guidelines developed by the international group of pathologists at the Pancreas Cancer Think Tank meeting sponsored by the National Cancer Institute and held in Park City, Utah in September 16–19, 1999. Briefly, PanIN-1A is an epithelial flat lesion, whereas PanIN-1B is a papillary or micropapillary lesion composed of tall columnar cells with basally located nuclei and abundant supranuclear mucin without cytological atypia. PanIN-2 is a mucinous, epithelial flat or papillary lesion with some nuclear abnormalities including loss of polarity, crowding, enlargement, nuclear stratification, and hyperchromatism. PanIN-3 is usually a papillary or micropapillary architecture with abnormal cribriforming, budding, and luminal necrosis with cytological abnormalities such as loss of nuclear polarity, dystrophic goblet cells, atypical mitotic figures, and macronucleoli. The presence of PanIN was evaluated on the slides of the normal pancreatic tissue at least 5 mm away from the carcinoma, while the non-neoplastic PanIN lesions were evaluated in the site of an ongoing disease process.

Immunohistochemistry

Tissue blocks were cut using a microtome into 5-µm-thick sections on silanized glass. The sections were deparaffinized in xylenes and hydrated in alcohols. In order to exhibit an antigen, the tissue sections were heated in a water bath at 99°C for 20 min and then cooled for 20 min at room temperature in citrate buffer (pH = 6.0). Then they were incubated with 0.5% hydrogen peroxide in methanol (Novocastra) to block endogenous peroxidase and next, with protein block (Novocastra) for 5 min. Incubation was performed with mouse Survivin antibody (R&D Systems AF886), rabbit anti-caspase-3 antibody (R&D Systems, AF835), for 1 h at room temperature. Following streptavidin-biotin reaction (biotinylated secondary antibody,

Table 2. Number of lesions assessed in the group of 70 patients

Normal pancreatic ducts	PanIN-1A (%)	PanIN-1B (%)	Total PanIN-1 (%)	PanIN-2 (%)	PanIN-3 (%)	Total (%)
35 (14.7%)	65 (27.2%)	67 (28.0%)	135 (55.2%)	51 (21.3%)	21 (8.8%)	239 (100%)

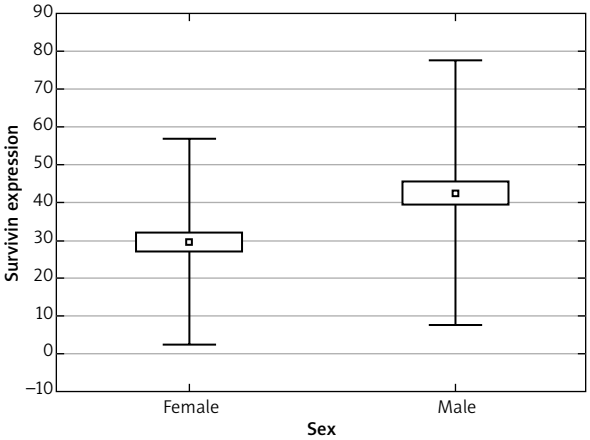

Figure 1. Differences in survivin expression by sex

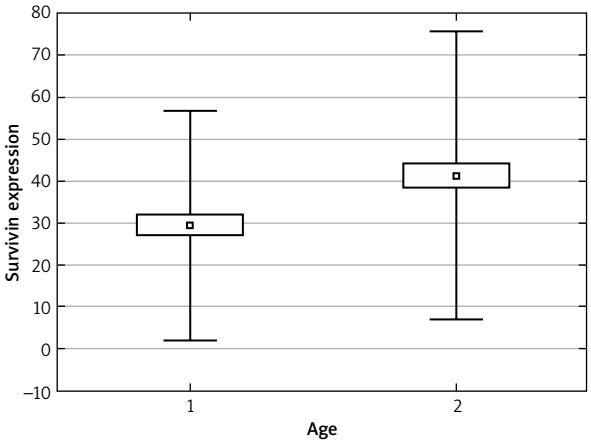

Figure 2. Differences in survivin expression by age

streptavidin-HRP; Novocastra), the antigen antibody complex was visualized by applying chromogen 3.3¢-diaminobenzidine (DAB, Novocastra). Positive and negative controls were performed according to the manufacturer's instructions. The protein expression levels were assessed in the pancreatic ductal epithelial cells using the quantitative method. Positively stained nuclei were counted in the epithelial cells in the normal pancreatic ducts and in the pancreatic ducts with various stages of pancreatic intraepithelial neoplasia and expressed as a percentage.

Statistical analysis

Statistica 10.0 (StatSoft, Cracow, Poland) was used for statistical analysis. The data were analyzed using Spearman's rank correlation test. Correlations between protein expression levels depending on the PanIN stage were tested using Mann-Whitney's test. A p-value of < 0.05 was considered statistically significant. Missing data were removed in pairs.

Results

The expression of caspase-3 and survivin and the age and sex of the examined patients, the location of the outbreak and the clinical unit in which a given outbreak was found were analyzed.

Associations of caspase-3 and survivin expression levels with the following factors were found: age of the patient, sex of the patient, location of the lesion, and the clinical department in which the lesion was observed.

There were statistically significant differences in survivin expression by sex ($p < 0.05$). In men, survivin levels were higher, with an average of 42%, while in women the levels were significantly lower (about 29%) (Figure 1). Regarding caspase-3, there were no significant differences in the expression level depending on gender. During the analysis of the obtained data, we also observed statistically significant differences in the level of survivin expression depending on age ($p < 0.05$). The expression of survivin in younger patients was significantly lower than in patients over 60 years of age (Figure 2). We did not find similar relationships with caspase-3. However, no significant differences were found in the expression levels of both survivin and caspase-3 with respect to the location of the lesions (head, body, tail). The relationships of the expression of survivin and caspase with the subtypes of individual PanINs and the type of pathology in patients who had undergone surgery (pancreatic cancer, CP, pancreatic cysts) were also assessed. No statistically significant differences were observed.

Survivin and caspase-3 expression and PanIN staging

There were statistically significant differences between both the levels of survivin and caspase-3 in accordance with the degree of PanIN. Thus, in healthy tissues, there was no expression of either survivin or caspase-3. In PanIN, the expression of either survivin or caspase-3 was significantly higher ($p < 0.05$). In regard to the expression level of both survivin and caspase-3, we observed significant differences depending on the severity of neoplasia. In the case of PanIN-1A, the mean survivin expression was 15%, and caspase-3 was 17%; in the case of PanIN-1B, the values reached 38.8% (survivin expression) and 26.9% (caspase-3), respectively. Concurring with the increase in the degree of PanIN, we observed a statistically significant increase in the expression of survivin and caspase. In PanIN 1B we observed a significantly higher level of survivin expression compared to the level of caspase-3, which is the opposite in the observation in PanIN-1A. The mean survivin expression in PanIN-2 was as high as 62.4%, and in PanIN-3 85.7%. In the case of caspase-3, statistically significantly higher expression was also observed (PanIN-2 36.1% vs. PanIN-3 54.3%), but these values were significantly lower than those observed with survivin. The relationships between survivin expression and the progres-

sion of the stage of neoplasia are presented in Figure 3. The expression of caspase-3 depending on the stage of PanIN is illustrated in Figure 4. Figure 5 presents the aggregated graphical distribution of the expression of both survivin and caspase-3 depending on the stage of intraepithelial pancreatic neoplasia.

Discussion

Pancreatic cancer remains one of the greatest challenges facing modern medicine. Despite the use of combined therapy and the development of diagnostic possibilities, it is often diagnosed late, which translates into its progression, and thus significantly reduces the therapeutic possibilities. This clearly affects the results of treatment – a relatively small number of resectable lesions and a low 5-year survival rate.

At present, there are no obvious tumor markers that can be assigned to pancreatic neoplasms. Similarly, there are no specific clinical symptoms: the most characteristic symptom is mechanical jaundice, but it is hard to call it an early symptom. Other pathologies, such as progressive malnutrition or diabetes, are also not observed in the early stages of the disease. Diabetes may precede the diagnosis of pancreatic cancer by several months.

Survivin and caspase-3 are proteins involved in the process of apoptosis. It is clinically significant that survivin is an inhibitor of this process. One of its actions is to "inhibit" proteins from the caspase family, which are involved in the proper course of apoptosis. In the available literature, these relationships are increasingly reported. So far, significantly higher tissue expression of survivin has been observed in lesions such as breast cancers, skin and eyeball cancers, and meningiomas [18–23]. Such observations have also been made in patients with gastrointestinal neoplasms: esophageal cancer, gastric cancer or pancreatic cancer. It seems justified to assume that the level of expression of both survivin and caspase-3 may affect the course of adjuvant therapy or the prognosis of patients. Vranic [18] suggested that the level of caspase-3 expression seems to be correlated with the degree of differentiation of the meningioma, and that it has an impact on relapse-free survival. More studies have been carried out on patients with breast cancer. Zhang *et al.* [21] compared the level of survivin expression in normal breast tissue (4.7%), to typical hypoplasia (5.4%), atypical ductal hypoplasia (42.7%), and patients with breast cancer (72.3%). Based on the available reports, it can be assumed that the level of survivin expression is related to the degree of differentiation of the lesion. Moreover, the thesis about the relationship between the clinical progression of the disease and the degree of survivin expression is also raised in some reports. Some authors also observed an increase in survivin expression, which was associated with the presence

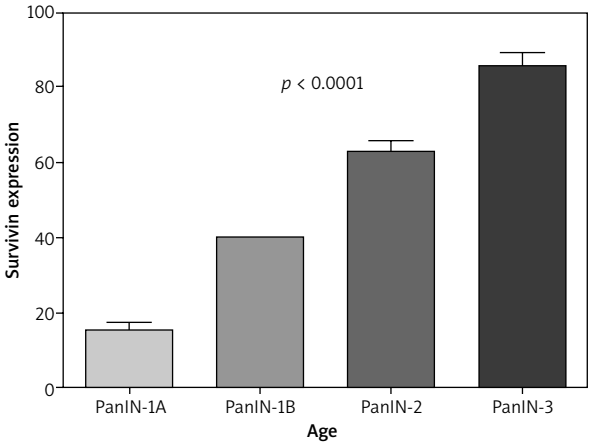

Figure 3. Comparison of survivin expression in various degrees of PanIN

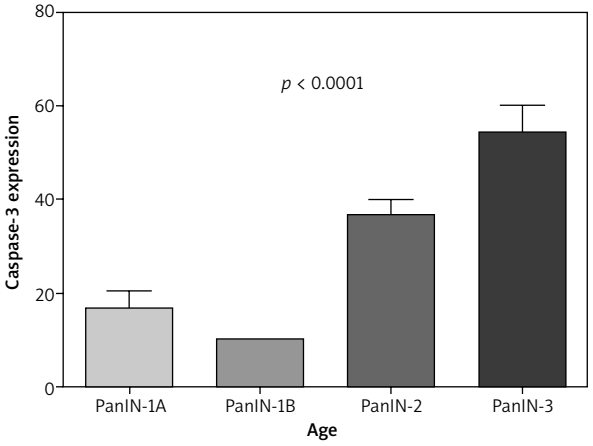

Figure 4. Comparison of caspase-3 expression in various degrees of PanIN

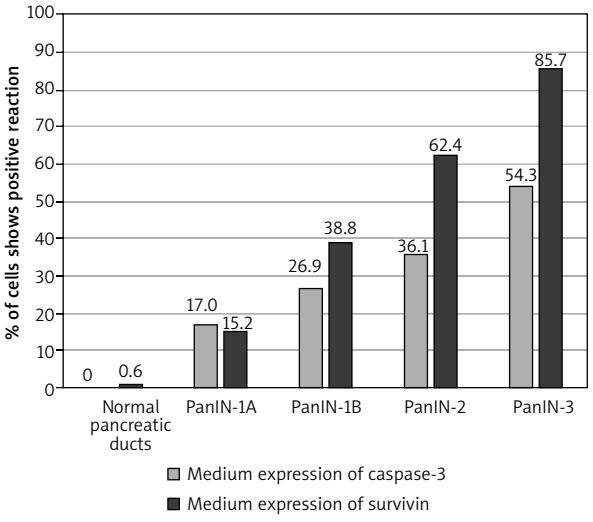

Figure 5. Graphical distribution of the expression of both survivin and caspase-3 depending on the stage of intraepithelial pancreatic neoplasia

of lymph node metastases [22–24]. On the other hand, the suggested correlation between the size of the primary tumor, overall survival and relapse-free survival and the level of survivin expression seems to be controversial. However, most authors pay attention to the relationship between the level of survivin and caspase-3 expression and the quality of response to adjuvant therapy (radio- and chemotherapy) [23–25]. There is a poor response to chemotherapy and radiation therapy in high expression of survivin and lower expression of caspase-3. Similar relationships were also found in stomach cancer, pancreatic cancer, and colorectal cancer. These observations had a significant impact on the direction of research towards new chemotherapy drugs. Hurtado *et al.* [25] presented their own research on new survivin inhibitors that can inhibit the growth of neoplastic cells in pancreatic cancer by inhibiting the transcription factors SP1 and SP3. The results presented by the authors are very encouraging. However, research on these inhibitors was performed *in vivo*, so it is not known how this will translate into clinical practice. In our research, we focused on the behavior of the expression level of survivin and caspase-3 in the case of pre-neoplastic changes, such as intraepithelial pancreatic neoplasia. We observed a clear increase in the level of survivin expression depending on the PanIN subtype. It seems to be related to the pathway of the progression of the carcinogenesis process, i.e. from the PanIN1 lesion to invasive cancer. The expression values for survivin increase from 15% for PanIN-1A to 85.7% for PanIN-3. The situation is similar for caspase-3, but here the increments are smaller. Simultaneously, our observations confirm the inhibitory effect of survivin on caspase-3. All these relationships can also be observed in the case of pancreatic cancer itself, i.e. the level of both survivin and caspase-3 expression is significantly higher in patients with these tumors than in healthy volunteers. The above dependencies begin to direct the research on new chemotherapy drugs. The inhibition of survivin, and thus stimulation of the action of proteins from the caspase family, seems to be one of the elements influencing the carcinogenesis process. This may have a significant impact on the therapeutic process in patients with diagnosed pancreatic cancer. We can already indirectly assume to what extent the patient will respond to the proposed chemotherapy, which, considering clinical experience and the previously presented statistics, will be an answer to the question not how, but: why so poorly? Another important issue seems to be breaking the chain of lesions leading from PanIN-1 to invasive carcinoma, and how to treat accidentally detected pancreatic intraepithelial neoplasia, especially PanIN-3. The behavior of the expression level of survivin and caspase-3, depending on the type of PanIN, observed in our research, and the expression level of these proteins in pancreatic cancer or other neoplasms, clearly indicate the confirmation of the sequence of events leading from PanIN-1 to invasive cancer.

Considering the lack of characteristic symptoms and, in turn, the late detection of pancreatic neoplasms, an effective and selective marker seems vital.

The present study certainly did not find such a marker. We also did not propose any potential solutions that would allow us to visualize the condition of the pancreas more accurately prior to surgery (PanIN foci are invisible in imaging tests or during surgery). After analyzing the results, the authors' attention is drawn to a group of patients with PanIN-3 foci, which were found both in pancreatic cancer, but also in patients with cystic lesions or with CP. While in the case of the first group, patients are categorized in terms of recurrence, patients after surgery due to CP or cysts are not under such strict control. The presence of PanIN-3 foci, as well as the high level of survivin and caspase-3 expression (which does not differ from the expression level of both proteins in cancer patients), makes us wonder whether we should monitor patients similarly to those after excision of a neoplastic lesion. We cannot recognize PanIN foci either intraoperatively or through visualization tests.

We believe that further studies are advisable, preferably on a larger number of patients with longer clinical observation, which could confirm or refute our thesis.

Study limitations

The relatively small number of respondents seems to be a basic problem. Another problem that should be mentioned is the inability to assess the presence of PanIN in visualization studies, but only they can be assessed post-factum in the material obtained intraoperatively. While conducting the study, the authors focused on comparing the expression of caspase-3 and survivin depending on the progression of PanIN. This expression was not compared depending on the underlying disease, because the above-mentioned research has confirmed the relationship between the expression of caspase-3 and survivin and cancer.

Conclusions

The expression levels of survivin and caspase-3 are inextricably linked to the progression of pancreatic intraepithelial neoplasia. The more advanced the neoplasia is, meaning the greater the damage of architectural and cytological atypia, the higher are the levels of survivin and caspase-3.

Conflict of interest

The authors declare no conflict of interest.

References

1. Rawla P, Sunkara T, Gaduputi V. Epidemiology of pancreatic cancer: global trends, etiology and risk factors. World J Oncol 2019; 10: 10-27.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
3. Hidalgo M, Cascinu S, Kleeff J, Labianca R, Lohr JM, Neoptolemos J, Real FX, Van Laethem JL, Heinemann V. Addressing the challenges of pancreatic cancer: future directions for improving outcomes. Pancreatology 2015; 15: 8-18.
4. Organization WH. World Cancer Report 2014. Accessed 06 October 2021.
5. United States National Cancer Institute. Pancreatic cancer: statistics 2018, May. Available from: https://www.cancer.net/cancer-types/pancreatic-cancer/statistics. Accessed 07 October 2018.
6. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, Negri E, Li D, Risch HA, Olson SH, Gallinger S, Miller AB, Bueno-de-Mesquita HB, Talamini R, Polesel J, Ghadirian P, Baghurst PA, Zatonski W, Fontham E, Bamlet WR, Holly EA, Bertuccio P, Gao YT, Hassan M, Yu H, Kurtz RC, Cotterchio M, Su J, Maisonneuve P, Duell EJ, Boffetta P, La Vecchia C. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol 2012; 23: 1880-1888.
7. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, Griffin C, Cameron JL, Yeo CJ, Kern S, Hruban RH. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004; 64: 2634-2638.
8. Murphy SJ, Hart SN, Lima JF, Kipp BR, Klebig M, Winters JL, Szabo C, Zhang L, Eckloff BW, Petersen GM, Scherer SE, Gibbs RA, McWilliams RR, Vasmatzis G, Couch FJ. Genetic alterations associated with progression from pancreatic intraepithelial neoplasia to invasive pancreatic tumor. Gastroenterology 2013; 145: 1098-1109.
9. Zińczuk J, Zaręba K, Guzińska-Ustymowicz K, Kędra B, Kemona A, Pryczynicz A. Expression of chosen cell cycle and proliferation markers in pancreatic intraepithelial neoplasia. Gastroenterology Rev 2018; 13: 118-126.
10. Misiura M, Zińczuk J, Zaręba K, Kamińska D, Guzińska-Ustymowicz K, Pryczynicz A. Actin-bundling proteins (actinin-4 and fascin-1) are involved in the development of pancreatic intraepithelial neoplasia (PanIN). Am J Med Sci 2020; 359: 147-155.
11. Brosens LA, Hackeng WM, Offerhaus GJ, Hruban RH, Wood LD. Pancreatic adenocarcinoma pathology: changing landscape. J Gastrointest Oncol 2015; 6: 358-374.
12. Distler M, Aust D, Weitz J, Pilarsky C, Grützmann R. Precursor lesions for sporadic pancreatic cancer: PanIN, IPMN, and MCN. Biomed Res Int 2014; 2014: 474905.
13. Kim GE, Bae HI, Park HU, Kuan SF, Crawley SC, Ho JJ, Kim YS. Aberrant expression of MUC5AC and MUC6 gastric mucins and sialyl Tn antigen in intraepithelial neoplasms of the pancreas. Gastroenterology 2002; 123: 1052-1060.
14. Biankin AV, Kench JG, Biankin SA, Lee CS, Morey AL, Dijkman FP, Coleman MJ, Sutherland RL, Henshall SM. Pancreatic intraepithelial neoplasia in association with intraductal papillary mucinous neoplasms of the pancreas: implications for disease progression and recurrence. Am J Surg Pathol 2004; 28: 1184-1192.
15. Westphal S, Kalthoff H. Apoptosis: targets in pancreatic cancer. Mol Cancer 2003; **2:** 6.
16. Wang Q, Zhang L, Yuan X, Ou Y, Zhu X, Cheng Z, Zhang P, Wu X, Meng Y, Zhang L. The relationship between the Bcl-2/Bax proteins and the mitochondria-mediated apoptosis pathway in the differentiation of adipose-derived stromal cells into neurons. PLoS One 2016; 11: e0163327.
17. Ambrosini G, Adida C, Altieri DC. A novel anti-apoptosis gene, survivin, expressed in cancer and lymphoma. Nat Med 1997; 3: 917-921.
18. Vranic A. Caspase-3 and survivin expression in primary atypical and malignant meningiomas. ISRN Neurosci 2013; 19: 26290.
19. Konstantinidou AE, Givalos N, Gakiopoulou H, Korkolopoulou P, Kotsiakis X, Boviatsis E, Agrogiannis G, Mahera H, Patsouris E. Caspase-3 immunohistochemical expression is a marker of apoptosis, increased grade and early recurrence in intracranial meningiomas. Apoptosis 2007; 12: 695-705.
20. Chakravarti A, Zhai GG, Zhang M, Malhotra R, Latham DE, Delaney MA, Robe P, Nestler U, Song Q, Loeffler J. Survivin enhances radiation resistance in primary human glioblastoma cells via caspase-independent mechanisms. Oncogene 2004; 23: 7494-7506.
21. Zhang M, Zhang X, Zhao S, Wang Y, Di W, Zhao G, Yang M, Zhang Q. Prognostic value of survivin and EGFR protein expression in triple-negative breast cancer (TNBC) patients. Target Oncol 2014; 9: 349-357.
22. Liu BB, Wang WH. Survivin and pancreatic cancer. World J Clin Oncol 2011; 2: 164-168.
23. Kami K, Doi R, Koizumi M, Toyoda E, Mori T, Ito D, Fujimoto K, Wada M, Miyatake S, Imamura M. Survivin expression is a prognostic marker in pancreatic cancer patients. Surgery 2004; 136: 443-448.
24. Bhanot U, Heydrich R, Möller P, Hasel C. Survivin expression in pancreatic intraepithelial neoplasia (PanIN): steady increase along the developmental stages of pancreatic ductal adenocarcinoma. Am J Surg Pathol 2006; 30: 754-759.
25. Hurtado M, Sankpal UT, Kaba A, Mahammad S, Chhabra J, Brown DT, Gurung RK, Holder AA, Vishwanatha JK, Basha R. Novel survivin inhibitor for suppressing pancreatic cancer cells growth via downregulating Sp1 and Sp3 transcription factors. Cell Physiol Biochem 2018; 51: 1894-1907.

Address for correspondence:

Konrad Zaręba MD, PhD
2nd Clinical Department of General,
Gastroenterological and
Oncological Surgery
Medical University of Białystok
M Skłodowskiej- Curie 24a
15-276 Białystok, Poland
Phone: +48 857 468 287
E-mail: konrad.zareba@umb.edu.pl

Received: 27.10.2022
Accepted: 26.02.2024
Online publication: 22.03.2024