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Research Progress on Apoptosis Inhibitory Protein Survivin and Its Application in Digestive Tract Tumors

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Abstract: The occurrence and development of tumor are closely related to the imbalance of apoptosis and proliferation regulation. Survivin is a newly discovered member of the apoptosis inhibitory protein (IAP) family with a unique structure. It is widely expressed in embryonic and developmental fetal tissues, with low or no expression in normal terminal differentiated adult tissues, while it is highly expressed in the vast majority of malignant tumor tissues. With the rapid development of molecular biology technology, a significant breakthrough has been made in the molecular mechanism of cell apoptosis. With the discovery that Survivin is involved in regulating two basic processes in cell life, namely inhibiting apoptosis and promoting cell proliferation, and playing a role in cell division and angiogenesis. The high expression of Survivin in malignant tumors indicates its important role in tumor production, apoptosis, and proliferation. The alimentary canal is one of the most common sites of human malignant tumors. In recent years, the incidence rate of alimentary canal tumors has been increasing year by year. Because of the early symptoms being not typical, it is easy to miss diagnosis, and most of them have entered the middle and late stages when diagnosed, which is easy to recur and metastasize, with a high fatality rate and serious harm to human health. Therefore, finding ideal tumor biomarkers for early diagnosis and monitoring prognosis is of great value. This article reviews the research progress of apoptosis inhibitor protein Survivin and its application in esophageal cancer, liver cancer and pancreatic cancer.

Keywords: Apoptosis Suppressor Protein, Survivin, Biological Characteristics, Esophageal Cancer, Liver Cancer, Pancreatic Cancer, Prognosis

1. Introduction

Survivin is currently the strongest inhibitor of apoptosis gene discovered and plays a crucial role in the process of cell apoptosis. Survivin mainly has important biological functions such as inhibiting cell apoptosis, participating in cell proliferation, division, and angiogenesis. It mainly acts through the terminal effector enzymes Caspase-3 and Caspase-7 that directly act on the cell apoptosis pathway, and is involved in cell cycle regulation and tumor angiogenesis [1]. Survivin is almost not expressed in normal adult tissues, but is highly expressed in most tumor tissues, which can inhibit tumor cell apoptosis, promote tumor cell proliferation, induce angiogenesis, and thereby increase the invasive ability of tumors [2]. Numerous studies have shown that Survivin is closely related to tumor apoptosis, proliferation, angiogenesis, and prognosis, especially at high levels in digestive tract tumors. It is speculated that it may be an oncogene involved in the occurrence and development of tumors, and is a potentially valuable tumor marker. The occurrence, development, recurrence, and metastasis of tumors are closely related to tumor angiogenesis. Reducing the generation of vascular

stimulating factors or enhancing the effect of vascular inhibitory factors can inhibit angiogenesis, thereby achieving the goal of inhibiting tumor growth. Therefore, inhibiting apoptosis and angiogenesis may become a new target for diagnosis and treatment of oncogene. To explore the relationship between apoptosis inhibitor protein Survivin and prognosis of digestive tract tumors is to provide necessary experimental and theoretical basis for diagnosis, treatment and prevention of digestive tract tumors.

2. Biological Characteristics of Survivin

2.1. Survivin Composition, Structure, Distribution and Localization

Survivin is an anti-apoptosis gene that is first screened and cloned from the human genome library by Ambrosini et al. of Yale University [3] in 1997. Survivin is included in the IAP family because it contains conserved sequence of the inhibitor of apoptosis protein (IAP) family. Survivin is an apoptosis inhibitor gene with strong effect found at present. The gene is located on chromosome 17q25, and the expressed product consists of 142 amino acid residues with a relative molecular weight of 16.5 KD [4] containing 4 exons and 3 introns. At present, 8 members of the human IAP family have been discovered, including NAIP (BIRC1), c-IAP1 (BIRC2), cIAP2 (BIRC3), XIAP (BIRC4), Survivin (BIRC5), Apollon (BIRC6), and Livin (BIRC7) [5]. With the continuous deepening of research, Survivin mRNA is cleaved and found to have 9 isomers with different anti apoptotic properties, such as survivin-2α, survivin-3β and survivin-2β (Retain intron 2 as exon), Survivin-δEx3 (exon 3 removed) contains 165 and 137 amino acids, respectively. Survivin- δ Ex3 retains most of its anti-apoptotic ability, which is similar in function to Survivin and has the function of inhibiting apoptosis, while survivin-2 α has the function of antagonizing Survivin and resisting apoptosis. Survivin-2 β has a cytotoxic effect and can significantly reduce its anti-apoptotic properties [6]. Survivin-δEx3 and survivin-2β having the opposite function, survivin-3 has received widespread attention from foreign scholars due to its unique functions and effects. There is relatively little research on the relationship between survivin-3β and tumors. There are also literature reports [7] that Survivin-δEx3 is mainly expressed in malignant tumors, while Survivin-2 β mainly expressed in benign tumors. There are three isomers of survivin-40, survivin-128, and survivin-140 present in human embryonic tissues. The latter also exists in thymus and testicular tissues, and there is no expression of survivin-40 in differentiated and mature tissues. Survivin-140 and Survivin-128, which only contain BIR structures, have the function of inhibiting caspase [6]. Survivin isomers have different biological activities, and the IAP family mainly exerts a wide range of anti-apoptotic functions by inhibiting the activity of caspase family members, playing different roles in different tumors.

Survivin is the smallest and strongest inhibitor of apoptosis in the apoptosis inhibitory protein family [8]. Its protein structure includes an N-terminal baculovirus IAP repeat (BIR) with inhibitory activity against cysteine aspartate specific protease (Caspase) and a long C-terminal alpha helix region, which plays a crucial role in apoptosis. Survivin protein has a very unique homologous dimer structure compared to other IAP protein molecules, and exists in the form of dimers in the cytoplasm. The Survivin in normal histiocyte is only expressed in the nuclei of G2/M phase of the cell cycle, while the Survivin in tumor cells is mainly present in the cytoplasm [5].

2.2. Function of Survivin and Its Mechanism of Inhibiting Apoptosis

The biological functions of Survivin mainly include inhibiting cell apoptosis, participating in cell cycle regulation and stress response, promoting cell proliferation, mitosis, and angiogenesis [9].

2.2.1. Inhibition of Apoptosis

Apoptosis, also known as programmed cell death (PDF), is an autonomous and orderly death that the body maintains in a stable internal environment, regulated by cells and regulated by pro apoptotic and anti- apoptotic gene proteins. The pathways of cell apoptosis mainly include internal pathways (mitochondrial mediated) and external pathways (death receptor mediated). Under normal circumstances, when cells are not stimulated by apoptotic signals, the expression of apoptotic proteins remains relatively stable. Once cells are stimulated by apoptotic signals, the expression of pro apoptotic genes and anti-apoptotic gene proteins is imbalanced, leading to cell apoptosis [10].

Survivin exerts a strong inhibitory effect on two cell apoptosis pathways mainly through direct protein binding and inhibition of upstream and downstream Caspases molecules. The Caspase family is a protease that promotes cell apoptosis, a key protein that mediates PDF, and a core regulatory factor for cell apoptosis. It plays a core role in the network of cell apoptosis mechanisms. Usually, Caspases exist in the cytoplasm in the form of pro-Caspase, and the activity of Caspase proenzyme is very low. It can be activated in different ways. Caspase proenzyme is activated by specific binding with reactants, releasing biologically active Caspases, which can also be activated by other Caspases. Activated Caspase is a key enzyme in cell apoptosis, which performs the function of cell apoptosis by specifically cleaving substrates. The Caspase family has 14 members, which are classified into inflammatory, apoptotic, and functionally unknown Caspases based on their biological functions [11]. The caspase family includes three types: apoptosis initiating factors (Caspase-2/8/9/10), apoptosis executing factors (Caspase-3/6/7), and inflammatory mediators, which together form a cascade reaction and have the effect of amplifying the reaction. By activating the upstream Caspases proenzyme starting protein and activating the executing protein Caspases3, cell apoptosis is ultimately achieved. Caspases-2 belongs to the initiating factor of apoptosis and plays a core role in triggering the apoptosis pathway after DNA damage in

cell models [12]. Caspases-3 is a key executor in regulating cell apoptosis and the most important terminal cleaving enzyme in the process of cell apoptosis. The research on its activation mechanism is of great significance for regulating the occurrence of cell apoptosis. Caspase-3 is located downstream of the caspase family, and two pathways converge at effector Caspase-3 and 7, mainly inhibiting the activation or catalytic activity of effector enzymes Caspase-3 and 7, and inhibiting both internal and external pathways. The inactive Caspases-3 zymogen is activated after receiving superior apoptosis stimulation, while the Caspases-9 zymogen is activated to activate downstream Caspases-3 to execute cell apoptosis. The activated Caspases-3 can further activate the Caspases-9 zymogen, thus forming a positive feedback regulation and accelerating the process of cell apoptosis [12]. Caspase-9 is an important apoptosis initiating factor in the mitochondrial transduction pathway, located upstream of the caspase pathway [13], and capapase-6 is located in the middle of the cascade reaction. After cleavage, the two are activated, activating downstream related Caspase proteins, initiating the apoptosis process, and being a key link in completing cell apoptosis [14], often serving as an important indicator of the degree of cell apoptosis. Caspase-8, as an apoptosis initiating factor in the death receptor transduction pathway, is located upstream of the cascade reaction, while Caspase-3 is located downstream of the Caspase-8 protein. The two are the most critical links in the death receptor transduction pathway, and their interactions together complete cell apoptosis. The occurrence of caspase-3 is an irreversible marker of apoptosis [15]. Therefore, Caspases-3 is one of the most important executors of apoptosis, and its expression level can reflect the situation of cell apoptosis.

Cell apoptosis is regulated by multiple factors such as pro apoptotic factors (caspase, wild-type p53, fas, etc.) and anti-apoptotic factors (Survivin, bcl-2, xIAP, etc.). Survivin overexpression can inhibit caspase, p53, and other induced cell apoptosis, bind specifically to caspase, inhibit caspase-3,7 activity, and block the occurrence of apoptosis; It can also indirectly inhibit caspase through p21 and bind to the cell cycle regulatory factor CDK4 to form the Survivin-CDK4 complex, releasing p21 from the CDK4 complex and then binding to mitochondrial Caspase-3 to inhibit its activity and block the process of cell apoptosis. The Bcl-2 family plays an important regulatory role in the mitochondrial apoptosis pathway and can induce cell apoptosis by activating downstream genes [16]. The endogenous pathway is regulated by the Bcl-2 family, which includes anti apoptotic genes Bcl-2, Bcl-xL, Bcl-w, Mcl-1, and pro apoptotic genes Bad, Bak, Bax, Bid, Bim. The Bcl-2/Bax ratio directly determines cell survival [17]. Bcl-2 family members are located on mitochondria, which can affect the permeability of mitochondria, cause the release of apoptosis inducing factors, and combine with Caspase-9 to form apoptotic bodies, further activate Caspase-3 to induce apoptosis. Research has found that the imbalance of cell apoptosis is related to the occurrence and development of tumors, and apoptosis related genes involved in cell apoptosis regulation are significantly correlated with tumors. Survivin is expressed to a certain extent in most tumor tissues and is associated with tumor recurrence and metastasis.

2.2.2. Participate in Cell Division and Proliferation

Survivin is a key factor in cell proliferation, closely related to cell proliferation, division, and cell cycle regulation by inhibiting cell apoptosis. Survivin is synthesized and degraded in normal tissues in a cell cycle dependent manner, with obvious cell cycle dependence. It is selectively expressed in G2/M phase of the cell cycle. At the beginning of mitosis, Survivin specifically binds to the spindle tubulin, which interferes with the normal progress of mitosis. Kobayashi et al. found that Survivin is expressed in all tissues with cell proliferation, and Survivin is regularly and widely expressed in embryonic tissues, participating in cell growth and differentiation [4]. The expression of Survivin in normal tissues significantly increases during the G2/M phase, thereby protecting the normal progression of mitosis. Survivin plays an important role in promoting cell cycle and accelerating cell division. Survivin is also involved in the regulation of chromosome segregation and plays an important role in chromosome and cytoplasmic division [18]. The expression of Survivin in tissues is cyclically dependent, mainly showing high expression in G2/M phase and low expression in G1 phase. This is related to the static state of the Survivin promoter in normal cells and its overexpression in tumor cells. The Survivin gene can promote tumor cell proliferation and differentiation by accelerating the transition of tumor cells from G1 to S phase and preventing tumor cells from recognizing apoptosis during G2/M phase. Therefore, Survivin is recognized as a tumor related gene [19].

2.2.3. Regulation of Angiogenesis

The formation of blood vessels is jointly regulated by pro angiogenic factors and anti-angiogenic factors. During the process of angiogenesis, various proangiogenic factors such as VEGF, basic fibroblast growth factor (bFGF), and angiopoietin-1 (Ang-1) promote endothelial cell proliferation by upregulating the expression of Survivin. O'Connor et al. [20] used VEGF and bFGF to induce quiescent endothelial cell division and detected the expression level of Survivin. They found that the content of Survivin in vascular endothelial cells increased by 16 times, suggesting that Survivin may be involved in regulating tumor angiogenesis. The Survivin gene can play an important role in the intermediate stages of angiogenesis through factors such as VEGF, bFGF, Ang-1, and COX-2 [10]. Controlling the expression or function of Survivin can affect pathological angiogenesis. Therefore, Survivin plays an important role in angiogenesis mediated by VEGF, and promotes tumor angiogenesis and tumor growth [21].

3. Significance of Survivin in Digestive Tract Tumors

The alimentary canal is one of the most common sites of

human malignant tumors. With the change of people's diet structure and lifestyle, the incidence rate of alimentary canal tumors is increasing year by year [22]. According to the latest global cancer statistics released by the American Cancer Society in 2011, the incidence rate and mortality of digestive tract tumors such as esophagus, stomach, liver, and colorectal all rank among the top 10 in developing countries [23]. Due to the atypical early symptoms of gastrointestinal tumors, most of them have entered the middle to late stages of diagnosis. The 5-year mortality rate after comprehensive treatment is over 90%, which seriously endangers human health. In recent years, clinical tests have been conducted to detect the expression and serum content of Survivin in digestive tract tumors, opening up new avenues for the diagnosis and prognosis testing of digestive tract tumors.

3.1. Significance of Survivin Expression in Esophageal Cancer Tissues

Esophageal cancer is one of the common malignant tumors of digestive tract in China. According to the statistical results of global tumor epidemiology data in 2018, the incidence rate and mortality of esophageal cancer in China account for 50% of the world [24]. The incidence of esophageal adenocarcinoma is increasing at a rate of more than six times annually, with a growth rate greater than any other cancer [25]. Approximately 150000 patients die from esophageal cancer each year, ranking fifth among all tumors [26]. Due to the relatively hidden early symptoms, most patients are already in the middle and late stages of diagnosis, with poor treatment effectiveness and prognosis, resulting in a high mortality rate [27]. Although the overall incidence rate of esophageal cancer in China is on the decline, it is still higher than the global average, and it is still one of the main malignant tumors threatening the health of Chinese residents [28]. Therefore, finding new diagnostic and treatment methods to improve patient survival is crucial.

Multiple researches on esophageal cancer have found a significant correlation between high expression of Survivin and poor prognosis. According to comprehensive foreign research data [29], Survivin can serve as a prognostic marker for esophageal cancer, and its overexpression can increase vascular invasiveness, resulting in poor prognosis. The level of Survivin mRNA in 96% of esophageal cancer tissues is significantly higher than that in normal esophageal tissues, and the positive rate of Survivin in advanced esophageal cancer tissues is 89%, which is associated with histological classification. Studies on subcellular localization of Survivin have shown an association between Survivin nuclear expression and 5-year survival and relapse free rates. The recurrence rate and mortality rate of Survivin nuclear expression increased by 2.95-fold and 2.74-fold, respectively. The expression rates of Survivin nucleus and cytoplasm in esophageal cancer tissue are 42% and 17%, respectively, with both nucleus and cytoplasm accounting for 30%. Survivin nucleus expression predicts an increase in long-term overall survival and recurrence free rate. Therefore, the prognostic value of Survivin nuclear expression in esophageal cancer tissue is still controversial. Kato et al. [30] believed that the average survival time of esophageal cancer patients with high expression of Survivin was significantly shorter than those with low expression of Survivin (9 months vs 30 months, P=0.0023). Therefore, Survivin protein expression can be an important prognostic indicator. Cao M et al. [31] found during follow-up that the recurrence rate of survivors with positive expression of Survivin in esophageal squamous cell carcinoma tissue was higher than those with negative expression, and the survival period is shorter. Zeng Jian et al. [32] also confirmed that esophageal cancer with positive Survivin expression was more prone to lymph node metastasis and has a higher degree of malignancy. Malhotra U et al. [33] used RT-PCR and Western blot methods to detect the expression of Survivin in fresh frozen tissues of esophageal adenocarcinoma (EAC) and/or cancer adjacent squamous epithelium (CASE), and found that the expression of Survivin in EAC tissue was significantly higher than that in CASE tissue of the same patient. The high expression of Survivin in EAC tissue was associated with an increased risk of recurrence and death. The 231G. C polymorphism (rs9904341 G. C) was commonly present in the promoter region of the Survivin gene, participating in the regulation of Survivin and increasing the susceptibility to gastrointestinal tract (GIT) cancer. Liu Y et al. [34] conducted a meta-analysis of 2231 GIT cancer patients and 2287 healthy controls, and found that Survivin 231G. C polymorphism was significantly associated with tumors, particularly increasing the risk of colorectal and gastric cancer, but the correlation with esophageal cancer was not high.

Zeng Yunzhu et al. [35] reported that the positive rate of survivin in esophageal cancer tissue was 74.5% (105/141) which was correlated with pathological T staging, lymph node metastasis, nerve bundle infiltration, and differentiation degree ($P<0.05$), but not with gender and age ($P>0.05$). It was suggested that Survivin was related to the invasion and distant metastasis of esophageal cancer. The later the tumor stage and the higher the malignancy, the higher the positive rate of Survivin. Survivin was positively correlated with the expression of VEGF-C and VEGFR-3 in esophageal cancer tissue. VEGF-C and VEGFR-3 were associated with lymph node metastasis in esophageal cancer. High expression of VEGF-C and VEGFR-3 suggested that esophageal cancer was accompanied by lymph node metastasis and poor prognosis. The combined detection of Survivin, VEGF-C, and VEGFR-3 in esophageal cancer was helpful for the early diagnosis of esophageal cancer, as well as the assessment of esophageal cancer invasion and lymph node metastasis, and the evaluation of prognosis [35]. Feng Min et al. [36] found that the expression of Survivin mRNA in Kazakh esophageal cancer tissues was higher than that in adjacent tissues (P=0.000), which was related to lymph node metastasis and clinical staging (P=0.042, 0.034). The expression of miR-143 was positively correlated with miR-145 (r=0.662, P=0.000) and negatively correlated with Survivin mRNA (r=-0.313, P=0.002), which suggested that miR-143, miR-145 were low expression and Survivin mRNA was high expression in

Kazakh esophageal cancer. The miR-143/145 gene cluster and Survivin mRNA may jointly participate in the carcinogenesis and development of Kazakh esophageal cancer. Wang Yang et al. [37] reported that the relative expression of miR-34a in esophageal cancer tissues was lower than that in adjacent tissues, while the positive rate and intensity distribution of Survivin expression were higher than those in adjacent tissues, with statistically significant differenced (P<0.05).

Hu Huiling et al. [38] investigated the regulatory effects of Survivin on Smad3 and PD-L1 in esophageal squamous cell carcinoma Eca109 cells and found that Survivin may affect the occurrence and development of esophageal cancer by participating in regulating tumor immune escape, providing reliable experimental and theoretical basis for targeted PD-L1 immunotherapy. The relative expression level of Survivin was significantly increased in the Survivin overexpression group of esophageal cancer patients, while the Survivin siRNA group and YM155 group significantly decreased the relative expression level of Survivin. The early apoptosis rate and total apoptosis rate were significantly increased in the Survivin siRNA group (P<0.05) 05). It suggested that Survivin was involved in the distribution and apoptosis regulation of esophageal cancer cell cycle [39]. Survivin underwent acetylation in esophageal cancer tissue and was closely related to the proliferation, invasion, and metastasis of esophageal cancer [40]. Survivin and acetyltransferase 2A (KAT2A) KAT2A proteins were highly expressed in esophageal cancer tissue, and there was a positive correlation between the two (r=0.517, P<0.05). The relative expression of Survivin and KAT2A mRNA and the acetylation rate of Survivin protein were significantly higher than those in adjacent tissues, which were related to TNM staging, differentiation, and lymph node metastasis of esophageal cancer (P<0.05) [41]. It was suggested that KAT2A was involved in the acetylation modification of Survivin during esophageal lesions, and its high expression may be an important early molecular event of Survivin acetylation modification, which had potential application value in the diagnosis and treatment of esophageal cancer.

3.2. Significance of Survivin Expression in Liver Cancer Tissues

Hepatocellular carcinoma (HCC) is the most common pathological type of primary liver cancer, which is ranking the second in the global mortality of malignant tumors, and whose incidence rate has increased in recent years [42]. Because of active angiogenesis, rapid proliferation, easy metastasis, and poor prognosis, it poses a serious threat to human life and health. Liver cancer patients have a high postoperative recurrence rate, which seriously affects survival rate [43]. Research has found that Survivin is highly expressed in liver cancer tissues and cell lines, and it has been confirmed that Survivin can serve as an important indicator for predicting the prognosis of liver cancer. Ikeguchi et al. [44] believed that the prognosis of HCC patients with negative expression of Survivin was significantly better than that of positive patients, which indicated that the expression of Survivin was closely related to the prognosis of HCC. Ye Chao et al. [45] found that the positive expression rate of Survivin in liver cancer tissue was 52.7% (29/55). The positive expression rate of Survivin in liver cancer with portal vein tumor thrombi or satellite nodules was significantly higher than that without portal vein tumor thrombi or satellite nodules. The recurrence rate/survival rate of Survivin positive liver cancer resection was significantly higher/lower than that of negative expression at 1 and 3 years after resection, and Survivin positive liver cancer resection was more prone to recurrence and death. Survivin is highly expressed in liver cancer tissue and almost all liver cancer cell lines such as HepG2 [46]. The positive rate of Survivin in liver cancer tissue was 70% (14/20) , Survivin expression was not found in both adjacent cancer tissues and liver cirrhosis tissues, which might serve as a diagnostic basis for early liver cancer.

Fang Yanqiu et al. [47] used immunohistochemistry, flow cytometry, and fluorescence quantitative PCR to detect the positive rate, protein, and gene levels of Survivin in liver cancer and adjacent tissues. They found that the positive expression rate of Survivin in liver cancer tissue (76.7%) was significantly higher than that in adjacent tissues (15%) and normal liver tissue (P<0.05), and the expression level of Survivin protein in adjacent tissues was also higher than that in normal liver tissue, but the difference was not statistically significant (P>0.05). The expression of Survivin protein in liver cancer tissue was related to the formation of portal vein tumor thrombi (P<0.05), but not to tumor size, capsule, alpha fetoprotein level, and HCC pathological staging (P<0.05). Dang Cunshu [48] found that the positive expression rate of Survivin in HCC tissue (80.0%, 32/40) was significantly higher than that in adjacent cancer tissue (27.5%, 11/40). Survivin expression was not found in normal liver tissue, with P<0.05. With the increase of HCC TNM staging, the positive expression rate of Survivin in cancer tissue and adjacent tissues showed an increasing trend (P<0.05). The expression of Survivin in HCC tissue and adjacent tissues was related to the TNM staging of tumors, which was of great significance for the diagnosis of HCC. Survivin expression was associated with a high risk of recurrence and poor prognosis after liver cancer resection. Most research results indicated that Survivin can be an important indicator for predicting the prognosis of liver cancer, but some scholars believed that Survivin had no significant impact on the evaluation of liver cancer prognosis [49].

Survivin mRNA is also an important indicator for predicting the prognosis of HCC. The positive rate of Survivin mRNA and protein in liver cancer tissue is 41% (21/51), which is not expressed in normal liver tissue. However, it is expressed in two adjacent tissues with severe liver fibrosis. It is speculated that Survivin mRNA expression may have the risk of cancer transformation, which is helpful for the early diagnosis of liver cancer. Survivin mRNA over-expression significantly promotes the recurrence rate of liver cancer. The survival rate decrease, and the recurrence rate (57%) of Survivin mRNA positive liver cancer patients is significantly higher than that of Survivin mRNA negative patients (19%). The 5-year survival rate (19%) is significantly lower than that

of negative patients (39%). The high expression level of Survivin mRNA in tumor tissue is expected to become a valuable indicator independent of clinical and pathological factors, and can be used for predicting the prognosis of HCC hepatectomy [49]. Yang Li et al. found that HCC patient Survivin whose positive expression rate of Ex3 mRNA was 58% (15/26), and the negative expression rate was 42% (11/26). Survivin mRNA expression was not observed in adjacent cancer tissues. Survivin in HCC organization whose expression of Ex3 was positively correlated with pathological tissue grading and TNM staging, but not with Survivin (P>0.05) [50]. Prompt Survivin- Δ Ex3 was significantly associated with the invasiveness and prognosis of HCC, and its apoptotic inhibitory effect was not affected by Survivin, which can serve as a potential predictive indicator for judging the invasiveness and progression of HCC. In recent years, research has found a close relationship between the Survivin gene and liver cancer. The Survivin gene is only expressed in liver cancer tissue, while it is not expressed in adjacent tissues and normal liver tissue (P<0.05). Survivin gene testing is helpful for early screening and prevention of HCC, and the content in liver cancer tissue is closely related to the occurrence, development, prognosis evaluation, and treatment effect of HCC [10], opening up a new pathway for the diagnosis of liver cancer susceptible populations.

Survivin combined with other indicators is more valuable in predicting the prognosis of HCC. NF-κB is an important nuclear transcription factor in eukaryotic cell and plays a very important role in cell proliferation, differentiation, tumor formation, invasion, metastasis and other processes [51]. Jin et al. [52] reported that the positive rates of Survivin and NF-κB in HCC tissues (75.7%, 231/305 and 79.0%, 241/305) were significantly higher than those in normal liver tissues (13.4%, 41/305 and 17.1%, 52/305, P<0.01). There was a significant positive correlation between the two expressions in HCC (P < 0.01). Survivin expression was correlated with tumor size, cyst invasion, portal vein thrombosis, and lymph node metastasis (P>0.05), but not with clinical stage of HCC (P<0.01). Survivin and NF-κB expression levels were associated with adverse prognostic factors. The survival of HCC patients with overexpression of Survivin and NF-κB protein was significantly shorter than that of negative HCC patients (P<0.01). Overexpressions of both Survivin and NF-κB were associated with reduced survival in HCC patients. Survivin was closely related to caspas-3, especially in promoting apoptosis. E Ying et al. [53] found that matrine can increase caspase-3 expression and decrease Survivin expression in human hepatoma cell line HepG2, and it can play a synergistic effect in combination with cisplatin and play a significant anticancer effect. Du Lianjiang et al. [54] reported that the positive rate of caspase-3 in HCC tissues (47.1%) was significantly lower than that in paracancer tissues (77.9%). The positive rate of lymph node metastasis (33.3%) was significantly lower than that of those without lymph node metastasis (62.0%). P < 0. 05). Multiple Logistic regression analysis showed that large tumor diameter, cirrhosis, lymph node metastasis and low Caspase-3 expression were risk factors for death in HCC patients. It was suggested that there were significant changes in gene level and protein expression in HCC tissues, providing valuable clues for the prevention and treatment of HCC. Most researches have shown that HCC tissue has significantly higher Survivin positive expression rate, protein content, and gene level than paracarcinoma tissue, which can be used for diagnosis and prognostic monitoring of HCC. Serum Survivin level combined with multiple indicators is more valuable for prognostic determination.

3.3. Significance of Survivin Expression in Bile Duct (Gallbladder) Cancer Tissue

Cholangiocarcinoma (CCA) is a malignant tumor originating from bile duct epithelial cells, and is the most common malignant tumor of the biliary tract. It ranks second only to HCC in liver malignancies [55]. In recent 30 years, the overall incidence rate of CCA has increased, but the 5-year survival rate after diagnosis and treatment has not increased accordingly [56]. Many tumor tissues have overexpression of Survivin, indicating that Survivin may be in a state of loss in tumor tissues. Liu Sanguang et al. [57] found that the positive expression rate of Survivin in CCA tissue was significantly higher than that in adjacent cancer tissues (79.2% vs 6.7%), indicating that the high expression of Survivin was involved in the process of CCA occurrence and development. Qin Xinglei et al. [58] reported that the expression rate of Survivin protein in extrahepatic cholangiocarcinoma tissues (67.8%, 40/59) was significantly higher than that in adjacent tissues (20.0%, 4/20), and its expression level was negatively correlated with differentiation degree, and positively correlated with TNM staging, lymphatic and neural infiltration, and lymph node metastasis. The average survival time (43.5 months) of the group with negative Survivin protein expression was twice as long as that of the positive group (21.1 months). The results of multivariate survival analysis showed that Survivin protein, cancer residue, and lymph node metastasis were independent prognostic factors after radical surgery for extrahepatic cholangiocarcinoma. Positive expression of Survivin protein suggested poor prognosis. The meta-analysis results showed [59] that Survivin protein was highly expressed in CCA tissue, with a positive rate (74.6%, 284/217) significantly higher than that in normal bile duct tissue (P<0.00001). There was a statistically significant difference in the expression of Survivin protein between high and low differentiation in CCA, as well as the presence or absence of lymph node metastasis (P=0.002). With the increase of clinical stage and the decrease of CCA differentiation degree, the positive expression rate of Survivin showed a decreasing trend. This indicates that Survivin was upregulated in CCA, and its high expression was involved in the occurrence and development of cholangiocarcinoma. The expression of survivin protein was related to the degree of differentiation, depth of invasion, clinical stage and lymph metastasis of CCA, which was expected to become an important indicator to judge the invasiveness and prognosis of CCA, and provide a new idea for gene targeting treatment of tumors.

The application of Survivin and other indicator detection in

CCA. The Fragile histidine triad (FHIT) gene is a tumor suppressor gene that exhibits transcriptional abnormalities, protein deletions, or low expression in various primary tumors and tumor cell lines. Xu Peng [60] found that the positive expression rate of FHIT in CCA tissue was lower than that in normal bile duct tissue adjacent to cancer, while the positive expression rate of Survivin was higher than that in normal bile duct tissue adjacent to cancer, with statistical significance (P<0.05). The expression of the two in CCA tissue was negatively correlated. The positive expression rate of Survivin was related to the differentiation degree, TNM staging, and lymph node metastasis of CCA tissue (P<0.05), and the overall survival time of patients with positive expression was significantly shorter than that of patients with negative expression (P=0.000). COX multivariate regression analysis showed that positive expression of FHIT and Survivin were independent factors for the prognosis of CCA (P<0.05), and there may be a synergistic effect on the occurrence of CCA.

Shuang Guoxin et al. [61] reported that Survivin was highly expressed in CCA tissue, but not in normal or benign bile ducts. The cell apoptosis index of the Survivin positive expression group in CCA tissue was significantly lower than that of the negative group (P<0.01). The expression of Bcl-2 in CCA tissue was also significantly higher than that in the control group. Survivin was positively correlated with Bcl-2 (P<0.01), and the expression of Survivin was correlated with lymph node metastasis. The expression rate of Bcl-2 increased with the increase of tissue differentiation, and there was no significant difference with TNM staging and lymph node metastasis. It may be related to the different pathways of action of the two in cell apoptosis. Li Yangjun et al. [62] reported that the positive rate of Survivin in CCA tissue (75.0%) was higher than that of Caspase-3 (40.0%), and the expression of the two in CCA was negatively correlated (r=-0.723, P<0.05), which was closely related to the degree of differentiation and lymph node metastasis (P<0.05). Survivin and NF in cholangiocarcinoma tissue- κ The positive rates of B and CD68 expression were significantly higher than those in the control group, and were closely related to the maximum diameter of the tumor- κ The positive rate of B was closely related to tumor metastasis and vascular involvement NF- κ. There was a positive correlation between B and CD68 expression. Indicating Survivin and NF in tumor cells of cholangiocarcinoma- κ. High expression of B and CD68 had a certain effect on tumor formation and progression [63]. Research [64] found that Survivin was a target gene for miRNA218, which was reduced in expression in CCA tissue and can increase apoptosis and inhibit invasion of CCA cells. miRNA-218 can negatively regulate CCA by interacting with Survivin's mRNA3'UTR.

Wan Yunle et al. [65] found that the positive expression rate of Survivin in gallbladder cancer tissue was 65.31% (32/49), which was significantly higher than that in gallbladder adenoma (0%), indicating that Survivin can play an important role in the occurrence and development of gallbladder cancer by inhibiting apoptosis of gallbladder cancer cells. However, the positive expression of Survivin in gallbladder cancer tissue was not related to its degree of differentiation, pathological grading, and metastasis, suggesting that Survivin expression may not be associated with the prognosis of gallbladder cancer. Shen Hanbin et al. [66] reported that the positive expression rates of Survivin, CD44v6, and nm23 in gallbladder cancer tissue were 66.7%, 56.4%, and 38.5%, respectively. The expression rates of Survivin and CD44v6 were significantly higher than those in adjacent cancer tissue and gallbladder adenomatous polyp tissue. The expression of CD44v6 and nm23 was related to tumor metastasis (P<0.05). The expression of Survivin and CD44v6 was upregulated, while the expression of nm23 was reduced and absent in gallbladder cancer tissue. It was suggested that Survivin, CD44v6, and nm23 have a synergistic effect on the pathogenesis of gallbladder cancer, jointly participating in the occurrence and development of gallbladder cancer, and promoting tumor metastasis.

3.4. Significance of Survivin Expression in Pancreatic Cancer

Pancreatic cancer is one of the most malignant tumors in digestive system with the worst prognosis. From 2005 to 2015, the incidence rate and mortality of male pancreatic cancer in China are higher than that of female, and that of urban is higher than that of rural [67]. The cancer statistics in 2020 show that the new cases of pancreatic cancer in the world account for the 14th in all malignant tumors, accounting for 2.6% of new malignant tumors. Based on the public data of the 2019 Global Burden of Disease Study (GBD2019), the change trend of incidence and death of pancreatic cancer is analyzed to use the join-point software. It is found that the incidence and death of pancreatic cancer in China show a significant upward trend from 1990 to 2019, especially among men and the elderly [68]. Pancreatic cancer is also the seventh leading cause of death for male and female malignant tumors worldwide, with a 5-year survival rate of only 9% [69]. This is related to late discovery and easy metastasis. The expression level of Survivin in pancreatic cancer is different from the research results of clinical case factors such as tumor clinical stage, histological grading, lymph node metastasis, etc. Satoh et al. [70] found that the positive expression rate of Survivin protein in pancreatic cancer tissue was 76.9%, and the expression of Survivin was up-regulated at the early stage, and was significantly related to apoptosis index.

Wang Yuling et al. [71] reported that the positive expression rate of Survivin mRNA in pancreatic cancer tissue was 74.2%, but it was not expressed in chronic pancreatitis and normal pancreatic tissue. There was a significant difference between the former and the latter (P<0.01); The expression of Survivin mRNA was related to the proliferative activity of pancreatic cancer. The PCNA index of Survivin positive patients [(46.4 ± 15.2)%] was significantly higher than that of Survivin negative patients [(28.4 ± 14.8)%, P<0.01], but there was no significant relationship between Survivin mRNA expression and the degree of differentiation, clinical stage, and lymph node metastasis of pancreatic cancer (P>0.05). Zhang Pengbo et al. [72] reported that the positive

rate of Survivin in pancreatic cancer tissues (70.0%, 21/30) was significantly higher than that in adjacent tissues (P<0 05). The expression of Survivin was not related to gender, age, tumor location, tumor size, and tumor differentiation (P>0 05), and significantly correlated with the presence or absence of lymph node metastasis, TNM staging [T (tumor infiltration range and degree), N (peripheral lymph node metastasis), and M (distant organ metastasis)] (P<0.05). Kaplan Meier survival analysis showed that the prognosis of the Survivin positive group was significantly worse than that of the negative group (P<0 05). These results suggested that Survivin play an important role in the development of pancreatic cancer in the elderly. According to Liu et al.'s report [73], the lower the degree of tumor differentiation, the higher the expression of Survivin. The results were consistent with those of the group without lymph node metastasis, which was significantly lower than that of the group with metastasis. It was suggested that Survivin expression was closely related to the poor prognosis of pancreatic cancer, and Survivin expression may be more aggressive. Shang Peizhong [74] reported that the positive rate of Survivin in primary pancreatic cancer tissue was 70.0% (49/70), while there was no expression in non tumor adjacent pancreatic tissue. Survivin expression was not related to gender, age and tumor site, but significantly related to tumor size, differentiation, TNM stage, lymph node metastasis, and survival period (P<0.05). It was suggested that the expression of Survivin was closely related to the clinicopathological indicators of pancreatic cancer, and its high expression indicates poor prognosis. It was confirmed that Survivin played a certain role in the occurrence and development of pancreatic cancer, and its expression was closely related to the malignant transformation of pancreatic epithelial cells. Sun Guogui et al. [75] Meta- analysis results showed that there was a statistically significant difference in the positive expression rate of Survivin between pancreatic cancer and the control group, whether there was lymph node metastasis, and clinical stages III+IV and I+II (P<0.001). High expression of Survivin increased the risk of pancreatic cancer, and could be used as a judgment indicator of pancreatic cancer lymph node metastasis and clinical stages. Liu et al. [76] Meta-analysis showed that the expression of Survivin was related to the poor prognosis of pancreatic cancer patients. The expression of Survivin in the cytoplasm might be a factor affecting the prognosis of pancreatic cancer, while the expression of Survivin in the nucleus had no significant impact on the poor prognosis of patients.

The application of Survivin and other indicators in pancreatic cancer. Survivin and X-linked inhibitor of apoptosis protein (XIAP) are two factors with the strongest inhibition of apoptosis in known IAPs. Almost all tumor cell lines have XIAP expression. The expression of XIAP in liver cancer, pancreatic cancer and other tissues is also higher than that in normal tissues, and is significantly related to the occurrence and development of tumors [77]. Some studies [78] found that XIAP and Survivin were highly expressed in pancreatic cancer tissue, and inhibiting their expression at the same time can significantly inhibit the proliferation of Panc-1 cells in pancreatic cancer, effectively reverse the apoptosis resistance of tumor cells, and enhance their chemosensitivity. It was suggested that the overexpression of survivin gene was related to the high proliferation of pancreatic cancer, played an important role in the development of pancreatic cancer, and was expected to become a new target for diagnosis and treatment of pancreatic cancer. Chen Zhongjian [79] reported that the expression rate of Survivin in pancreatic islet vessel element carcinoma (88.2%) was significantly higher than that in pancreatic islet cell carcinoma (11.9%) and pancreatic islet cell tumor (6.3%) (P<0.01). The expression rate of Ki-67 in pancreatic vessel element carcinoma (93.7%) was significantly higher than that in pancreatic cell carcinoma. The expression rate of Ki-67 in pancreatic islet cell carcinoma was lower (5.3%). There was almost no expression in pancreatic islet cell tumor (P<0.01). The expression of Ki-67 and Survivin was not related to the patient's age, gender, and cancer tissue location (P>0.05). The higher the degree of differentiation of pancreatic cancer, the lower the expression rate of Ki-67, and the higher the expression rate of lymph node metastasis (P<0.05). The expression rates of Survivin and Ki-67 in pancreatic cancer tissues were both increased, and were related to the degree of differentiation and lymph node metastasis. Survivin can be used as a prognostic indicator of pancreatic cancer.

Zhao Su et al. [80] found that the positive expression rates of Survivin and caspase 3 in pancreatic cancer tissues were significantly higher than those in adjacent tissues (P There was no significant difference in the positive expression rates of survivin and caspase-3 in pancreatic cancer tissues at TNM stage and in pancreatic cancer tissues with different lymph node metastases (P>0.05). These results suggested that Survivin and caspase 3 were highly expressed in pancreatic cancer tissue, and were closely related to the occurrence and development of pancreatic cancer, and played an important role in promoting tumor cell infiltration. The positive expression of Survivin was related to the degree of lymph node metastasis and differentiation, while caspase 3 may participate in the early pathogenesis of pancreatic cancer, and has little effect on late and distant metastasis.

4. Conclusion

A large number of clinical and experimental research results have confirmed that Survivin, as the strongest factor in inhibiting apoptosis, is highly expressed in digestive tract malignant tumor tissues. The positive expression rate, protein level, and gene content of Survivin are significantly higher than those of the control group. It is not only related to the onset of tumors, but also closely related to disease progression and prognosis. However, the research results are not entirely the same, and there are even opposing views, which require conducting large-scale prospective studies to reach consensus. Serological indicators have important reference value in early screening and prognostic evaluation of gastrointestinal malignant tumors. Combined detection of multiple indicators has greater prognostic monitoring value for gastrointestinal

malignant tumors. Based on the principles of evidence-based laboratory medicine, it is imperative to screen 3-4 indicators such as Survivin for prognostic monitoring of gastrointestinal malignant tumors with high sensitivity and specificity. This will provide new indicators for the screening of gastrointestinal tumors and simple, fast, and valuable indicators for prognostic monitoring.

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