World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
doi:10.5306/wjco.v2.i3.164

World J Clin Oncol 2011 March 10; 2(3): 164-168
ISSN 2218-4333 (online)

REVIEW

Survivin and pancreatic cancer

Bin-Bin Liu, Wei-Hong Wang

Bin-Bin Liu, Wei-Hong Wang, Department of Gastroenterology, Peking University First Hospital, Beijing 100034, China
Author contributions: Liu BB and Wang WH contributed equally to this paper.
Correspondence to: Wei-Hong Wang, Professor, Department of Gastroenterology, Peking University First Hospital, Beijing 100034, China. wangweihong@medmail.com.cn
Telephone: +86-10-83572616 Fax: +86-10-66518105
Received: September 27, 2010 Revised: December 3, 2010
Accepted: December 10, 2010
Published online: March 10, 2011

Abstract

Pancreatic cancer is estimated to be the fourth most common cancer in men and fifth in women in the world and has poor prognosis. In recent years, more and more effort has been put on the relationship between pancreatic cancer and apoptosis. As a newly discovered inhibitor of apoptosis, survivin has drawn more attention. Strong evidence has shown that survivin is expressed in pancreatic cancer cells on frozen sections. Survivin increases in the development of pancreatic ductal adenocarcinoma and its expression can be a marker in evaluating the prognosis of pancreatic cancer patients. Survivin itself may be a new target in the treatment of pancreatic cancer and a survivin DNA vaccine could generate specific antitumor effects in pancreatic carcinoma models.

Key words: Survivin; Pancreatic cancer; Tumor suppression

Peer reviewer: Jose M Cuezva, Professor of Biochemistry and Molecular Biology, Centro de Biologia Molecular Severo Ochoa, Universidad Autonoma de Madrid, c/ Nicolas Cabrera, 1, 28049, Madrid, Spain

Liu BB, Wang WH. Survivin and pancreatic cancer. *World J Clin Oncol* 2011; 2(3): 164-168 Available from: URL: http://www.wjgnet.com/2218-4333/full/v2/i3/164.htm DOI: http://dx.doi.org/10.5306/wjco.v2.i3.164

INTRODUCTION

Pancreatic cancer is estimated to be the fourth most common cancer in men and fifth in women in the world. Despite the development of surgical resection, radiotherapy and chemotherapy, the prognosis is poor since 5-year survival after surgery in patients with resectable disease is approximately 15% to 20%[1]. The effort for new targets in the treatment of pancreatic cancer has drawn more and more attention recently.

Inhibition of apoptosis is very important in the development of cancer. Inhibitor of apoptosis can not only accelerate the development of tumor but also promote the resistance to therapy. Survivin is a new member of inhibitor of apoptosis (IAP) family. It is a 16.5 kDa protein and highly conserved. It contains only one baculovirus IAP repeat and lacks a carboxyl-terminal RING finger, which makes survivin different from other IAP proteins. Survivin protein functions to inhibit caspase activation, thereby leading to negative regulation of programmed cell death (apoptosis). It can also partially inhibit the cell death induced by Fas and Bax[2,3] and now is considered as a mitotic regulator[4,5]. As a newly-discovered IAP, survivin is found to be expressed in many carcinomas, including human cancers of lung, colon, pancreas, prostate and breast[2,3]. Strong expression of survivin can also be found in some apoptosis-regulated fetal tissues, including the stem cell layer of stratified epithelia, endocrine pancreas, and thymic medulla. It is also expressed in human fetal lung, liver, heart, kidney, and gastrointestinal tract, which may contribute to tissue homeostasis and differentiation[6]. However, no survivin is detected in normal terminally differentiated adult tissues[2]. The levels of survivin are low in resting endothelial cells and could be up-regulated on activation to proliferate. Vascular endothelial-cadherin (VE-cadherin) expression is believed to be one of the factors to maintain low levels of

survivin in endothelial cells[7]. More studies have focused on the relationship between pancreatic cancer and survivin.

EXPRESSION OF SURVIVIN IN PANCREATIC CANCER

Satoh *et al*[8] found survivin expressed in 76.9% cases of pancreatic duct cell adenocarcinoma (PDC) and 56.3% intraductal papillary-mucinous tumor (IPMT) lesions. Malignant tumors expressed survivin more frequently than benign tumors. In PDC, the increased expression of survivin was accompanied with the reduction of apoptotic index in tumor cells. Sarela *et al*[9] also reported that survivin was expressed in majority of pancreatic adenocarcinomas tested and correlated with both cellular proliferation and apoptosis. Yang *et al*[10] investigated three pancreatic cancer cell lines and found high expression of survivin in these tumor cells.

Jinfeng *et al*[11] investigated twenty-two lesions from patients with IPMT, including 12 benign ones (IPMT adenoma) and 10 malignant ones (4 IPMT Carcinoma in Situ [CIS] and 6 invasive IPMT lesions), and found the expression of survivin and p53 increased in the development from IPMT adenoma to IPMT CIS with the reduction of apoptosis in tumor cells. The results suggest that survivin and p53 may promote the progress from benign lesions to malignant ones.

Studies indicate that survivin may become a future marker for pancreatic cancer cells in frozen sections. Yang *et al*[12], synthesized molecular beacons (MBs, short hairpin oligonucleotide probes which can bind to specific oligonucleotide sequences and show fluorescent signals) targeting transcripts of mutant K-ras and survivin, and examined the specificity for detecting the two genes in pancreatic cancer cells using a fluorescence imaging-based technique. Survivin MBs were found binding to survivin gene and a bright fluorescent signal was produced specifically in pancreatic cancer cells. In frozen sections of pancreatic cancer tissues, survivin MBs were also found to have a high specificity in identifying cancer cells. The results provide pathologists a new choice for detecting pancreatic cancer cells in frozen sections, and may be used in clinical practice in the future. However, Jhala *et al*[13] investigated the biomarkers in diagnosing pancreatic carcinoma using fine needle aspirates and found that survivin expression was not a good marker for separating reactive ductal cells from pancreatic adenocarcinoma.

Increased expression of survivin is also reported in the development of pancreatic ductal adenocarcinoma (PDA). Bhanot *et al*[14] used laser capture microdissection, real-time polymerase chain reaction and immunohistochemistry to measure transcriptional levels of survivin and its protein expression in normal pancreatic ducts, pancreatic intraepithelial neoplasia (PanIN) and PDA. A steady increase in mRNA and protein expression of survivin was found from low-grade lesions (PanINs-1) to high-grade lesions (PanINs-2 and 3) and further to PDA. The results indicate that survivin may promote the changing process and could be a signal for malignant lesions.

SURVIVIN EXPRESSION AS A MARKER FOR EVALUATING PROGNOSIS

Specimens from pancreatic cancer patients who accepted surgery with or without postoperative radiation therapy (PORT) were assessed and the relationship between the expression of survivin and the prognosis was evaluated. Patients with positive survivin expression had shorter survival time than those who had no survivin expression, whereas PORT had no impact on survival time in both survivin positive patients and survivin negative patients. The research indicates that survivin may become a prognostic marker for pancreatic cancer[15].

The study of Grabowski *et al*[16] also showed that nuclear survivin expression was a potent prognostic marker for shorter survival time in gastroenteropancreatic neuroendocrine tumor disease. Determination of nuclear survivin expression may be used to individualize therapeutic strategies. Survivin has been shown to reside in mitochondria, nucleus and cytosol of tumors[17,18]. Tonini *et al*[19] made the first study on the prognostic relevance of survivin expression in pancreatic cancer in relation with its intracellular distribution. They investigated nuclear and cytoplasmic expression of survivin in 67 patients with pancreatic cancer and reported that patients with high nuclear survivin expression had a longer survival time, while patients with high cytoplasmic survivin expression had a shorter survival time. The median survival time for patients with positive nuclear expression was 27 mo while for patients with negative nuclear expression it was only 10 mo. However, the median survival for patients with positive cytoplasmic expression was 10 months compared with 25 months for patients with negative cytoplasmic expression. In other malignant tumors, such as colorectal cancer, cytoplasmic survivin overexpression is also associated with a poor prognosis, while nuclear survivin overexpression is associated with a better one. The mechanisms for the intracellular distribution of survivin in human cancer cells are still unclear; however, determination of the different expression of survivin may make a new marker for evaluating the prognosis of patients with pancreatic cancer[20].

Theodoropoulos *et al*[21], investigated survivin gene polymorphisms and the characteristics of pancreatic cancer. The genotypes of the survivin promoter are GG, CC and CG. The frequency of the 31G/C polymorphism was investigated in 80 patients with pancreatic cancer and 160 controls. A significant relationship was found between survivin C carrier and the advanced T stage accompanied with the presence of lymph node metastasis, indicating that the status of survivin C carriage was related to more aggressive features of the tumor.

SIGNIFICANCE OF SURVIVIN EXPRESSION IN THE TREATMENT OF PANCREATIC CANCER

The expression of survivin may be associated with the route of metastasis and the sensitivity to chemotherapy for

patients with pancreatic cancer. Lee *et al*[22] investigated 49 cases of pancreatic cancer and found that 93.9% of them were positive for survivin expression. In patients with positive expression of survivin, perineural invasion was more common; while in patients with negative expression of survivin, venous invasion seemed more common. These findings suggest that survivin may be associated with perineural or venous invasion, which indicate the metastatic route. However, the reason for the relationship between survivin expression and invasion mode is not clear. Among these patients, 14 received epirubicin, cisplatin and 5-FU combination chemotherapy. Patients with lower expression of survivin were more sensitive to the chemotherapeutic protocol. The results suggest that survivin may be used as a potential predictive marker in chemotherapy.

Expression of survivin is also a radioresistance factor in patients with pancreatic cancer. Asanuma *et al*[23] found an inverse relationship between survivin mRNA expression and radiosensitivity in 5 pancreatic cancer cell lines using a quantitative RT-PCR, indicating that survivin may act as a radioresistance factor in pancreatic cancer cells. They also found that the survivin mRNA increased significantly after X-ray irradiation, implying that survivin was an inducible radioresistance factor in pancreatic cancer cells. Further results of this study suggest that survivin expression directly down-regulates radiosensitivity[24].

Studies also reveal that down-regulation of survivin diminishes radioresistance of pancreatic cancer cells. Kami *et al*[25] evaluated the effect of short interfering RNA (siRNA) directly against survivin expression in radioresistant cells (AsPC-1). The activity of the survivin promoter and the expression of survivin mRNA were examined in 3 pancreatic cancer cell lines. Various levels of survivin mRNA and the transcriptional activity of the survivin promoter were found in pancreatic cancer cells, and both of them correlated with the radiosensitivity of tumor cells. On the other hand, radiation could increase the activity of the survivin promoter and mRNA expression in these cells. However, siRNA treatment markedly decreased the expression of survivin mRNA in AsPC-1 cells, and diminished the radioresistance of pancreatic cancer cells. These results indicate that combined therapy of a survivin inhibitor and radiation may be effective in the treatment of pancreatic cancer.

Guan *et al*[26] also proved that down regulation of survivin expression by small interfering RNA induced apoptosis in pancreatic cancer cells (cell line PC-2) and enhanced its radioactivity. The sequence-specific siRNA markedly decreased survivin mRNA and protein, which resulted in apoptosis in 7.03% of cells treated with siRNA. However, apoptosis was found in 14.58% of cells treated with siRNA combined with radiation, and only 1.66% of cells were found to be apoptotic in the radiation group. These studies give us new hope in the treatment of pancreatic cancer.

In spite of more and more new aggressive therapies, resistance of many tumors to current therapeutic protocols is still a formidable problem. Thus more and more attempts to improve the effects of treatment for cancer patients now depend on methods targeting the resistance of tumor cells[27]. Survivin may be a new target in the treatment of pancreatic cancer. Fulda *et al*[28] used survivin antisense oligonucleotides down-regulating the expression of survivin, and revealed tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) induced apoptosis was sensitized in many tumor cells. The cells they used included neuroblastoma, medulloblastoma, glioblastoma, melanoma, pancreatic carcinoma, prostate carcinoma, and breast carcinoma cells. They also found that G1 arrest was associated with less expression of survivin and sensitization for TRAIL-induced apoptosis.

Liang *et al*[29] tried survivin as a new target for pancreatic cancer gene therapy. A 10'-23' anti-survivin mRNA DNAzyme was designed, synthesized and delivered into human pancreatic carcinoma cell PANC-1 through liposomes, and the influence on the growth of PANC-1 cells was evaluated. The results showed that with the destruction of the mRNA substrate of survivin by DNAzyme, apoptosis of PANC-1 was increased and cell growth was inhibited. The designed DNAzyme against survivin mRNA is a promising candidate for gene therapy of human pancreatic carcinoma. Liu *et al*[30] also proved that human pancreatic cancer cell transfected with a siRNA plasmid expression vector against survivin showed decreased cell growth, spontaneous apoptosis, and a specific G0/G1 arrest accompanied with the reduction of survivin mRNA and protein. In addition, the chemosensitivity of pancreatic cancer cells to gemcitabine was increased markedly after suppressing the expression of survivin. Guan *et al*[31] proved that knockdown of survivin expression by siRNA could suppress proliferation of human pancreatic cancer cell PC-2. The research of Tsuji *et al*[32] also suggested that survivin-specific siRNA deserved further investigation as a new approach for the treatment of cancer.

Shen *et al*[33] performed experiments inhibiting the growth of cancer cells by silencing survivin not only *in vitro* but also *in vivo*. In their study, they designed and constructed a short hairpin RNAs (shRNAs) specific to survivin, cloned it into a plasmid vector, and transfected the recombinant plasmids into a human pancreatic cancer cell line Patu8988. The proliferation rates of the cancer cells were reduced markedly when transfected with the survivin-shRNA plasmids. When Patu8988 cells with survivin-shRNA were inoculated into BALB/c nude mice, the growth of the tumor was lower and the size of the tumor was smaller compared with the control group. The results showed that vector-based survivin-shRNAs could inhibit the expression of survivin in human pancreatic cancer Patu8988 cells and ultimately inhibit cell proliferation both *in vitro* and *in vivo*. Thus, knockdown expression of survivin may be a future way to treat pancreatic cancer.

Encouraging results have also been obtained in humans. Wobser *et al*[34] used survivin-based peptide vaccinations consisting of a modified HLA-A2 restricted survivin epitope on a 72-year old patient who suffered from pancreatic cancer with liver metastasis. The patient got partial remission of liver metastasis under vaccination with survivin peptides and later a complete remission with a dura-

tion of 8 mo. Although the disease relapsed 6 mo after vaccination stopped, it was the first case of a successful use of survivin-based vaccination, which threw light on the gloomy prognosis of advanced pancreatic cancer.

It has been reported that survivin DNA vaccine generates specific antitumor effects in pancreatic carcinoma in mouse models. Human or mouse survivin DNA was given to a murine pancreatic cancer model and the effect of the vaccination was evaluated. Slower tumor growth and longer lifetime were found in mice vaccinated with survivin DNA, no matter whether it was from human or mouse source. Greater infiltration of lymphocytes was found in tumors of the immunized mice. The research showed that survivin DNA vaccination could generate specific antitumor effects with increased lymphocyte infiltration at the tumor sites, and both xenogeneic survivin and congeneric ones had the same immune response[35].

Now more and more attention is being paid to the relationship between apoptosis and pancreatic cancer, including its development and therapy. As a novel IAP member, survivin inhibits caspase activity thereby negatively regulating apoptosis, which draws more attention in the study of cancer. Further studies of survivin should provide a new choice for the marker in diagnosis and the target treatment of the disease.

REFERENCES

1 **Grover S**. Blueprints pocket gastroenterology. Pancreatic Cancer. Lippincott Williams & Wilkins, 2007: 166-169
2 **Ambrosini G**, Adida C, Altieri DC. A novel anti-apoptosis gene, survivin, expressed in cancer and lymphoma. *Nat Med* 1997; **3**: 917-921
3 **Tamm I**, Wang Y, Sausville E, Scudiero DA, Vigna N, Oltersdorf T, Reed JC. IAP-family protein survivin inhibits caspase activity and apoptosis induced by Fas (CD95), Bax, caspases, and anticancer drugs. *Cancer Res* 1998; **58**: 5315-5320
4 **Uren AG**, Wong L, Pakusch M, Fowler KJ, Burrows FJ, Vaux DL, Choo KH. Survivin and the inner centromere protein INCENP show similar cell-cycle localization and gene knockout phenotype. *Curr Biol* 2000; **10**: 1319-1328
5 **Bourhis E**, Hymowitz SG, Cochran AG. The mitotic regulator Survivin binds as a monomer to its functional interactor Borealin. *J Biol Chem* 2007; **282**: 35018-35023
6 **Adida C**, Crotty PL, McGrath J, Berrebi D, Diebold J, Altieri DC. Developmentally regulated expression of the novel cancer anti-apoptosis gene survivin in human and mouse differentiation. *Am J Pathol* 1998; **152**: 43-49
7 **Iurlaro M**, Demontis F, Corada M, Zanetta L, Drake C, Gariboldi M, Peiro S, Cano A, Navarro P, Cattelino A, Tognin S, Marchisio PC, Dejana E. VE-cadherin expression and clustering maintain low levels of survivin in endothelial cells. *Am J Pathol* 2004; **165**: 181-189
8 **Satoh K**, Kaneko K, Hirota M, Masamune A, Satoh A, Shimosegawa T. Expression of survivin is correlated with cancer cell apoptosis and is involved in the development of human pancreatic duct cell tumors. *Cancer* 2001; **92**: 271-278
9 **Sarela AI**, Verbeke CS, Ramsdale J, Davies CL, Markham AF, Guillou PJ. Expression of survivin, a novel inhibitor of apoptosis and cell cycle regulatory protein, in pancreatic adenocarcinoma. *Br J Cancer* 2002; **86**: 886-892
10 **Yang L**, Cao Z, Yan H, Wood WC. Coexistence of high levels of apoptotic signaling and inhibitor of apoptosis proteins in human tumor cells: implication for cancer specific therapy. *Cancer Res* 2003; **63**: 6815-6824
11 **Jinfeng M**, Kimura W, Sakurai F, Moriya T, Takeshita A, Hirai I. Histopathological study of intraductal papillary mucinous tumor of the pancreas: special reference to the roles of Survivin and p53 in tumorigenesis of IPMT. *Int J Gastrointest Cancer* 2002; **32**: 73-81
12 **Yang L**, Cao Z, Lin Y, Wood WC, Staley CA. Molecular beacon imaging of tumor marker gene expression in pancreatic cancer cells. *Cancer Biol Ther* 2005; **4**: 561-570
13 **Jhala N**, Jhala D, Vickers SM, Eltoum I, Batra SK, Manne U, Eloubeidi M, Jones JJ, Grizzle WE. Biomarkers in Diagnosis of pancreatic carcinoma in fine-needle aspirates. *Am J Clin Pathol* 2006; **126**: 572-579
14 **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
15 **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
16 **Grabowski P**, Griss S, Arnold CN, Hörsch D, Göke R, Arnold R, Heine B, Stein H, Zeitz M, Scherübl H. Nuclear survivin is a powerful novel prognostic marker in gastroenteropancreatic neuroendocrine tumor disease. *Neuroendocrinology* 2005; **81**: 1-9
17 **Fortugno P**, Wall NR, Giodini A, O'Connor DS, Plescia J, Padgett KM, Tognin S, Marchisio PC, Altieri DC. Survivin exists in immunochemically distinct subcellular pools and is involved in spindle microtubule function. *J Cell Sci* 2002; **115**: 575-585
18 **Dohi T**, Beltrami E, Wall NR, Plescia J, Altieri DC. Mitochondrial survivin inhibits apoptosis and promotes tumorigenesis. *J Clin Invest* 2004; **114**: 1117-1127
19 **Tonini G**, Vincenzi B, Santini D, Scarpa S, Vasaturo T, Malacrino C, Coppola R, Magistrelli P, Borzomati D, Baldi A, Antinori A, Caricato M, Nuzzo G, Picciocchi A. Nuclear and cytoplasmic expression of survivin in 67 surgically resected pancreatic cancer patients. *Br J Cancer* 2005; **92**: 2225-2232
20 **Qi G**, Tuncel H, Aoki E, Tanaka S, Oka S, Kaneko I, Okamoto M, Tatsuka M, Nakai S, Shimamoto F. Intracellular localization of survivin determines biological behavior in colorectal cancer. *Oncol Rep* 2009; **22**: 557-562
21 **Theodoropoulos GE**, Michalopoulos NV, Panoussopoulos SG, Taka S, Gazouli M. Effects of caspase-9 and survivin gene polymorphisms in pancreatic cancer risk and tumor characteristics. *Pancreas* 2010; **39**: 976-980
22 **Lee MA**, Park GS, Lee HJ, Jung JH, Kang JH, Hong YS, Lee KS, Kim DG, Kim SN. Survivin expression and its clinical significance in pancreatic cancer. *BMC Cancer* 2005; **5**: 127
23 **Asanuma K**, Moriai R, Yajima T, Yagihashi A, Yamada M, Kobayashi D, Watanabe N. Survivin as a radioresistance factor in pancreatic cancer. *Jpn J Cancer Res* 2000; **91**: 1204-1209
24 **Asanuma K**, Kobayashi D, Furuya D, Tsuji N, Yagihashi A, Watanabe N. A role for survivin in radioresistance of pancreatic cancer cells. *Jpn J Cancer Res* 2002; **93**: 1057-1062
25 **Kami K**, Doi R, Koizumi M, Toyoda E, Mori T, Ito D, Kawaguchi Y, Fujimoto K, Wada M, Miyatake S, Imamura M. Downregulation of survivin by siRNA diminishes radioresistance of pancreatic cancer cells. *Surgery* 2005; **138**: 299-305
26 **Guan HT**, Xue XH, Dai ZJ, Wang XJ, Li A, Qin ZY. Downregulation of survivin expression by small interfering RNA induces pancreatic cancer cell apoptosis and enhances its radiosensitivity. *World J Gastroenterol* 2006; **12**: 2901-2907
27 **Peto J**. Cancer epidemiology in the last century and the next decade. *Nature* 2001; **411**: 390-395
28 **Fulda S**, Debatin KM. Sensitization for tumor necrosis factor-related apoptosis-inducing ligand-induced apoptosis by the chemopreventive agent resveratrol. *Cancer Res* 2004; **64**: 337-346
29 **Liang Z**, Wei S, Guan J, Luo Y, Gao J, Zhu H, Wu S, Liu T. DNAzyme-mediated cleavage of survivin mRNA and inhi-

bition of the growth of PANC-1 cells. *J Gastroenterol Hepatol* 2005; **20**: 1595-1602
30 **Liu WS**, Yan HJ, Qin RY, Tian R, Wang M, Jiang JX, Shen M, Shi CJ. siRNA directed against survivin enhances pancreatic cancer cell gemcitabine chemosensitivity. *Dig Dis Sci* 2009; **54**: 89-96
31 **Guan HT**, Xue XH, Wang XJ, Li A, Qin ZY. Knockdown of survivin expression by small interfering RNA suppresses proliferation of two human cancer cell lines. *Chin Med Sci J* 2006; **21**: 115-119
32 **Tsuji N**, Asanuma K, Kobayashi D, Yagihashi A, Watanabe N. Introduction of a survivin gene-specific small inhibitory RNA inhibits growth of pancreatic cancer cells. *Anticancer Res* 2005; **25**: 3967-3972
33 **Shen YM**, Yang XC, Song ML, Qin CH, Yang C, Sun YH. Growth inhibition induced by short hairpin RNA to silence survivin gene in human pancreatic cancer cells. *Hepatobiliary Pancreat Dis Int* 2010; **9**: 69-77
34 **Wobser M**, Keikavoussi P, Kunzmann V, Weininger M, Andersen MH, Becker JC. Complete remission of liver metastasis of pancreatic cancer under vaccination with a HLA-A2 restricted peptide derived from the universal tumor antigen survivin. *Cancer Immunol Immunother* 2006; **55**: 1294-1298
35 **Zhu K**, Qin H, Cha SC, Neelapu SS, Overwijk W, Lizee GA, Abbruzzese JL, Hwu P, Radvanyi L, Kwak LW, Chang DZ. Survivin DNA vaccine generated specific antitumor effects in pancreatic carcinoma and lymphoma mouse models. *Vaccine* 2007; **25**: 7955-7961

S- Editor Cheng JX **L- Editor** O'Neill M **E- Editor** Ma WH