

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 October 21; 23(39): 7059-7200



**REVIEW**

- 7059** Less common etiologies of exocrine pancreatic insufficiency

*Singh VK, Haupt ME, Geller DE, Hall JA, Quintana Diez PM*

**MINIREVIEWS**

- 7077** Radiofrequency ablation for hepatic hemangiomas: A consensus from a Chinese panel of experts

*Gao J, Fan RF, Yang JY, Cui Y, Ji JS, Ma KS, Li XL, Zhang L, Xu CL, Kong XL, Ke S, Ding XM, Wang SH, Yang MM, Song JJ, Zhai B, Nin CM, Guo SG, Xin ZH, Lu J, Dong YH, Zhu HQ, Sun WB*

**ORIGINAL ARTICLE****Basic Study**

- 7087** Detection of *KRAS* G12D in colorectal cancer stool by droplet digital PCR

*Olmedillas-López S, Lévano-Linares DC, Aúz Alexandre CL, Vega-Clemente L, León Sánchez E, Villagrasa A, Ruiz-Tovar J, García-Arranz M, García-Olmo D*

- 7098** Optimal timing for the oral administration of Da-Cheng-Qi decoction based on the pharmacokinetic and pharmacodynamic targeting of the pancreas in rats with acute pancreatitis

*Zhang YM, Zhu L, Zhao XL, Chen H, Kang HX, Zhao JL, Wan MH, Li J, Zhu L, Tang WF*

**Retrospective Study**

- 7110** Short- and long-term results of endoscopic ultrasound-guided transmural drainage for pancreatic pseudocysts and walled-off necrosis

*Watanabe Y, Mikata R, Yasui S, Ohyama H, Sugiyama H, Sakai Y, Tsuyuguchi T, Kato N*

- 7119** Laparoscopic finding of a hepatic subcapsular spider-like telangiectasis sign in biliary atresia

*Zhou Y, Jiang M, Tang ST, Yang L, Zhang X, Yang DH, Xiong M, Li S, Cao GQ, Wang Y*

- 7129** Digestive tract reconstruction using isoperistaltic jejunum-later-cut overlap method after totally laparoscopic total gastrectomy for gastric cancer: Short-term outcomes and impact on quality of life

*Huang ZN, Huang CM, Zheng CH, Li P, Xie JW, Wang JB, Lin JX, Lu J, Chen QY, Cao LL, Lin M, Tu RH, Lin JL*

**Observational Study**

- 7139** Adalimumab efficacy in enteropathic spondyloarthritis: A 12-mo observational multidisciplinary study

*Luchetti MM, Benfaremo D, Ciccio F, Bolognini L, Ciferri M, Farinelli A, Rossini M, Mosca P, Triolo G, Gabrielli A*

- 7150** Presence of columnar-lined esophagus is negatively associated with the presence of esophageal varices in Japanese alcoholic men  
*Yokoyama A, Hirata K, Nakamura R, Omori T, Mizukami T, Aida J, Maruyama K, Yokoyama T*
- 7160** Characteristics and outcomes of cholangiocarcinoma by region in Thailand: A nationwide study  
*Chaiteerakij R, Pan-ngum W, Poovorawan K, Soonthornworasiri N, Treeprasertsuk S, Phaosawasdi K*
- 7168** Expression of annexin A5 in serum and tumor tissue of patients with colon cancer and its clinical significance  
*Sun CB, Zhao AY, Ji S, Han XQ, Sun ZC, Wang MC, Zheng FC*

### **CASE REPORT**

- 7174** Faecal microbiota transplantation in patients with *Clostridium difficile* and significant comorbidities as well as in patients with new indications: A case series  
*Lahtinen P, Mattila E, Anttila VJ, Tillonen J, Teittinen M, Nevalainen P, Salminen S, Satokari R, Arkkila P*
- 7185** Oval mucosal opening bloc biopsy after incision and widening by ring thread traction for submucosal tumor  
*Mori H, Kobara H, Guan Y, Goda Y, Kobayashi N, Nishiyama N, Masaki T*
- 7191** Evidence from a familial case suggests maternal inheritance of primary biliary cholangitis  
*Shin S, Moh IH, Woo YS, Jung SW, Kim JB, Park JW, Suk KT, Kim HS, Hong M, Park SH, Lee MS*

### **LETTERS TO THE EDITOR**

- 7198** Duplicate publication bias weakens the validity of meta-analysis of immunosuppression after transplantation  
*Fairfield CJ, Harrison EM, Wigmore SJ*

**ABOUT COVER**

Editorial board member of *World Journal of Gastroenterology*, İlhami Yüksel, MD, Associate Professor, Gastroenterology, Yildirim Beyazıt University School of Medicine, Ankara 06100, Turkey

**AIMS AND SCOPE**

*World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7<sup>th</sup>, 14<sup>th</sup>, 21<sup>st</sup>, and 28<sup>th</sup> each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

**INDEXING/ABSTRACTING**

*World Journal of Gastroenterology* (*WJG*) is now indexed in Current Contents<sup>®</sup>/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch<sup>®</sup>), Journal Citation Reports<sup>®</sup>, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports<sup>®</sup> cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29<sup>th</sup> among 79 journals in gastroenterology and hepatology (quartile in category Q2).

**FLYLEAF**

**I-IX Editorial Board**

**EDITORS FOR THIS ISSUE**

**Responsible Assistant Editor:** Xiang Li  
**Responsible Electronic Editor:** Yan Huang  
**Proofing Editor-in-Chief:** Lian-Sheng Ma

**Responsible Science Editor:** Ze-Mao Gong  
**Proofing Editorial Office Director:** Jin-Lei Wang

**NAME OF JOURNAL**  
*World Journal of Gastroenterology*

**ISSN**  
ISSN 1007-9327 (print)  
ISSN 2219-2840 (online)

**LAUNCH DATE**  
October 1, 1995

**FREQUENCY**  
Weekly

**EDITORS-IN-CHIEF**  
**Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon**, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

**Stephen C Strom, PhD, Professor**, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

**Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology**, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach,

CA 90822, United States

**EDITORIAL BOARD MEMBERS**  
All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

**EDITORIAL OFFICE**  
Jin-Lei Wang, Director  
Yuan Qi, Vice Director  
Ze-Mao Gong, Vice Director  
*World Journal of Gastroenterology*  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLISHER**  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpoffice@wjgnet.com](mailto:bpoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>

<http://www.wjgnet.com>

**PUBLICATION DATE**  
October 21, 2017

**COPYRIGHT**  
© 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

**SPECIAL STATEMENT**  
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

**INSTRUCTIONS TO AUTHORS**  
Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

**ONLINE SUBMISSION**  
<http://www.f6publishing.com>

## Observational Study

# Expression of annexin A5 in serum and tumor tissue of patients with colon cancer and its clinical significance

Chong-Bing Sun, Ai-Yan Zhao, Shuai Ji, Xiao-Qing Han, Zuo-Cheng Sun, Meng-Chun Wang, Fu-Chang Zheng

Chong-Bing Sun, Ai-Yan Zhao, Xiao-Qing Han, Zuo-Cheng Sun, Meng-Chun Wang, Fu-Chang Zheng, Department of General Surgery, Weifang People's Hospital, Weifang 261000, Shandong Province, China

Shuai Ji, Department of Anorectal Surgery, Linqu People's Hospital, Weifang 261000, Shandong Province, China

Author contributions: All authors contributed to the manuscript.

Institutional review board statement: This study is approved by the Local Hospital Review Board.

Informed consent statement: All cases enrolled have signed the consent statement.

Conflict-of-interest statement: No conflict of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Dr. Fu-Chang Zheng, Associate Chief Physician, Department of General Surgery, Weifang People's Hospital, 151 Guangwen Road, Weifang 261000, Shandong Province, China. [zhengfc@yeah.net](mailto:zhengfc@yeah.net)  
Telephone: +86-536-8192599

Received: February 27, 2017

Peer-review started: February 27, 2017

First decision: April 10, 2017

Revised: June 20, 2017

Accepted: August 8, 2017

Article in press: August 8, 2017

Published online: October 21, 2017

## Abstract

### AIM

To investigate the expression of annexin A5 in serum and tumor tissue of patients with colon cancer and to analyze its clinical significance.

### METHODS

Ninety-three patients with colon cancer treated at our hospital between February 2013 and March 2016 were included in an observation group, and 40 healthy individuals were included in a control group. Enzyme-linked immunosorbent assay was performed to determine the serum level of annexin A5, while immunohistochemistry was performed to determine the expression of annexin A5 in cancer tissues.

### RESULTS

The serum level of annexin A5 was  $0.184 \pm 0.043$  ng/mL in the observation group, which was significantly higher than that in the control group ( $P < 0.05$ ). Annexin A5 expression was detected in 79.31% of the patients with lymph node metastasis, which was significantly higher than that in patients without lymph node metastasis ( $P < 0.05$ ). Moreover, annexin A5 expression was detected in 86.96% of the patients with stage III to IV disease, which was significantly higher than that in patients with stage I to II disease ( $P < 0.05$ ). The serum level of annexin A5 was  $0.215 \pm 0.044$  ng/mL in patients whose tumors were positive for annexin A5 expression, which was significantly higher than that in patients whose tumors were negative for annexin A5 expression ( $P < 0.05$ ). The serum level of annexin A5 was correlated with annexin A5 expression in colon cancer tissues ( $r$



= 0.312,  $P < 0.05$ ). When a cutoff value of  $> 0.148$  ng/mL for serum level of annexin A5 was used in the diagnosis of colon cancer, the sensitivity was 83.90%, and the specificity was 57.50%.

### CONCLUSION

For patients with colon cancer, annexin A5 expression in cancer tissues is related to lymph node metastasis and tumor grade. Serum level of annexin A5 is related to annexin A5 expression in cancer tissues and is of diagnostic relevance.

**Key words:** Immunohistochemistry; Annexin A5; Colon cancer; Serum

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** For patients with colon cancer, annexin A5 expression in cancer tissues is related to lymph node metastasis and tumor grade. Serum level of annexin A5 is related to annexin A5 expression in cancer tissues and is of diagnostic relevance.

Sun CB, Zhao AY, Ji S, Han XQ, Sun ZC, Wang MC, Zheng FC. Expression of annexin A5 in serum and tumor tissue of patients with colon cancer and its clinical significance. *World J Gastroenterol* 2017; 23(39): 7168-7173 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i39/7168.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i39.7168>

## INTRODUCTION

Colon cancer is a common malignancy of the digestive tract. Studies have shown that the incidence of colon cancer is  $\geq 0.005\%$ <sup>[1]</sup> and that the incidence has continued to trend upwards in recent years because of risk factors such as diet and smoking<sup>[2,3]</sup>.

Basic cancer research has shown that changes in the levels of certain molecules affect tumor cell proliferation and differentiation, which in turn affect the development and progression of malignant tumors<sup>[4]</sup>. Annexin A5, first isolated from human placenta, was found to bind to phosphatidylserine in a calcium-dependent manner<sup>[5,6]</sup>. In the present study, 93 patients with colon cancer who were treated at our hospital between February 2013 and March 2016 were included to investigate the expression of annexin A5 in serum and in cancer tissues, with an aim to investigate its clinical significance.

## MATERIALS AND METHODS

### General information

Ninety-three patients with colon cancer (observation group) who were treated at our hospital between

February 2013 and March 2016 were included in this study. The inclusion criteria were as follows: (1) pathologically confirmed colon cancer; (2) complete clinical and pathological data; and (3) being willing to provide informed consent. The exclusion criterion was incomplete clinical or pathological data. Forty healthy individuals who underwent a routine health checkup at our hospital were included as controls. No significant difference was observed with respect to age or gender between the two groups (Table 1).

### Detection of serum level of annexin A5

A fasting venous blood sample was collected from each subject in the morning and centrifuged at 10000 r/min to separate the serum, which was then stored at  $-20^{\circ}\text{C}$  and tested within one week to determine the annexin A5 level. The Roche automated biochemical analyzer E170 module was used for testing, and the assay kit was purchased from Shanghai Taikang Biotechnology Co., Ltd. The assay was performed according to the instructions given in the package insert. Control serum or standard was included with the kit.

### Immunohistochemistry

Paraffin sections were deparaffinized, rehydrated, and cut into 3 mm sections. The sections were incubated in 3%  $\text{H}_2\text{O}_2$  at room temperature for 5 min, rinsed with deionized water (3 min  $\times$  3 times), blocked with 10% milk protein (1 g protein in 100 mL of purified water), and incubated at room temperature for 5 min. Next, the sections were incubated with a mouse anti-annexin A5 antibody (Nanjing Biyuntian Biotechnology Co., Ltd.) for 2 h at  $37^{\circ}\text{C}$ , followed by a PBS wash (5 min  $\times$  3 times). Then, the slides were incubated with a horseradish peroxidase-labeled rabbit secondary antibody (Roche) for 30 min at  $37^{\circ}\text{C}$ , followed by a PBS wash (5 min  $\times$  3 times). After that, the slides were incubated with NBT/BCIP reagent, which was used to develop the reaction, for 5 min. Finally, the sections were counterstained, dehydrated, cleared, mounted, and observed under an OLIPICS microscope (Shanghai Precision Instrument Co., Ltd). All the required reagents were purchased from Nanjing Taikang Biotechnology Co., Ltd.

### Evaluation criteria for immunohistochemical staining

Immunohistochemical staining was considered positive if yellow granules were present in the cytoplasm of tumor cells or stromal cells. The staining intensity was graded as follows: 0, no staining; 1, light yellow; 2, yellow; and 3, brown. The percentage of positive cells was scored as follows: 0,  $< 5\%$ ; 1, 5% to 24%; 2, 25% to 50%; 3, 51% to 74%; and 4, and  $\geq 75\%$ . The product of the staining intensity and the percentage of positive cells was either  $< 2$  (negative) or  $\geq 2$  (positive).

**Table 1** General information (mean  $\pm$  SD)

Group	n	M/F	Age (yr)
Observation group	93	54/39	53.29 $\pm$ 9.49
Control group	40	27/13	52.17 $\pm$ 8.14
$t/\chi^2$		1.046	0.65
P value		> 0.05	> 0.05

**Table 2** Relationship between Annexin A5 and clinicopathological features of patients with colon cancer n (%)

Clinicopathological feature	n	Positive	$\chi^2$	P value
Gender				
M	54	31 (57.41)	0.023	> 0.05
F	39	23 (58.97)		
Age, yr			0.516	> 0.05
$\geq$ 55	47	29 (61.70)		
< 50	46	25 (54.35)		
Lymph node metastasis			7.812	< 0.05
Yes	29	23 (79.31)		
No	64	31 (48.44)		
Tumor diameter (cm)			0.067	> 0.05
$\geq$ 5	51	29 (56.86)		
< 5	42	25 (59.52)		
Tumor stage			31.204	< 0.05
I to II	47	14 (29.79)		
III to IV	46	40 (86.96)		

**Table 3** Serum levels of Annexin A5 in the two groups (mean  $\pm$  SD, ng/mL)

Group	n	Annexin A5	t	P value
Observation group	93	0.184 $\pm$ 0.043	2.904	< 0.05
Control group	40	0.159 $\pm$ 0.051		

### Statistical analysis

SPSS v19.0 was used for statistical analyses. Measurement data are expressed as mean  $\pm$  SD and were analyzed by the *t*-test. Count data were analyzed by the  $\chi^2$  test. Spearman rank correlation analysis was performed to analyze potential correlations between variables. A receiver operating characteristic curve was used to analyze the diagnostic value of serum annexin A5 level.  $P < 0.05$  was considered statistically significant.

## RESULTS

### Annexin A5 expression in cancer tissue

No significant difference was observed in the positive expression rates of annexin A5 among patients of different ages or genders, or those with different tumor diameters. Moreover, 79.31% of the patients with lymph node metastasis expressed annexin A5, which was significantly higher than the percentage of patients without lymph node metastasis ( $P < 0.05$ ); 86.96% of the patients with stage III to IV disease expressed annexin A5, which was significantly higher

than the percentage of patients with stage I to II disease ( $P < 0.05$ ) (Table 2).

### Serum levels of annexin A5 in the two groups

The serum level of annexin A5 was significantly higher in the observation group than in the control group ( $P < 0.05$ ) (Table 3).

### Correlation between serum level of annexin A5 and expression of annexin A5 in tumor tissue

The serum level of annexin A5 was 0.215  $\pm$  0.044 ng/mL in patients whose colon tumors were positive for annexin A5 expression, which was significantly higher than the corresponding value in patients whose colon tumors were negative for annexin A5 (0.180  $\pm$  0.021 ng/mL) ( $t = 4.599$ ,  $P < 0.05$ ). A Spearman rank correlation analysis showed that the serum level of annexin A5 was related to the expression of annexin A5 in tumor tissues ( $r = 0.312$ ,  $P < 0.05$ ).

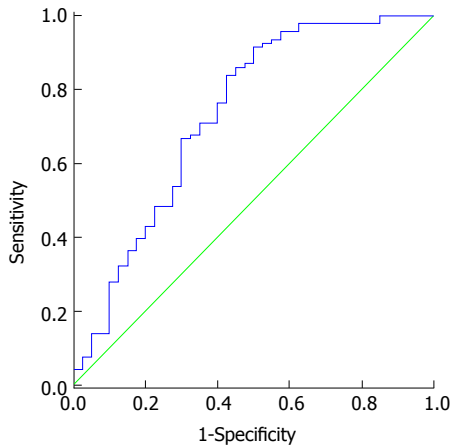
### Diagnostic value of serum level of annexin A5

The ROC curve for the serum level of annexin A5 in the diagnosis of colon cancer showed an area under the curve of 0.732 ( $P < 0.05$ ). At a cutoff value of 0.148 ng/mL, the sensitivity was 83.90%, and the specificity was 57.50% (Figure 1).

## DISCUSSION

Changes in diet, excessive alcohol consumption, and genetic susceptibility factors promote the development and progression of colon cancer. In particular, among elderly male smokers aged 45 or older, the incidence of colon cancer is 0.005% or higher and has continued to trend upwards in recent years<sup>[7,8]</sup>. For colon cancer, the incidence of early metastasis is high, which results in poor patient outcomes: the five years survival rate is < 35%, and the median survival time is < 32 mo<sup>[9-11]</sup>. Studies on the genetic and biological mechanisms of the development and progression of colon cancer may provide new targets for immune therapy or strategies of comprehensive biological therapy for colon cancer<sup>[12,13]</sup>.

Molecular changes play an important regulatory role in the development of malignant tumors. Cell surface Connexins or membrane proteins can induce the transcription initiation activity of downstream oncogenes, which promotes aberrant activation of the cell cycle in colonic epithelial cells and leads to excessive proliferation of cancer cells<sup>[14]</sup>. Accumulating experimental data indicate that phosphatidylserine exposition is associated with apoptosis and other cell death programs<sup>[15-17]</sup>, which renders it an attractive target in imaging overall cell death. Annexin A5 is identified in blood vessel as a blood anticoagulation factor and it builds voltage-dependent calcium channel in phosphatidylserine bilayers<sup>[18,19]</sup>. Corsten *et al*<sup>[20]</sup> showed that through binding with strong affinity to phosphatidylserine, annexin A5 offers an interesting opportunity for visualization of aggregate



**Figure 1** Receiver operating characteristic curve for the value of serum level of annexin A5 in the diagnosis of colon cancer.

cell death<sup>[21,22]</sup>, thus providing a fit benchmark for *in vivo* monitoring of anticancer treatment<sup>[23-26]</sup>. Recently, annexin A5 has been reported as a new mediator of cisplatin-induced apoptosis by inducing voltage-dependent anion channel oligomerization in human kidney epithelial cells<sup>[27,28]</sup>. Annexin A5 forms N6-acetyllysine at specific positions of the amino-terminal region of the membrane protein, and as a result, it affects the formation of a transcriptional co-inhibitory complex and participates in transcriptional repression and silencing of tumor suppressor genes via H1 phosphorylation<sup>[29,30]</sup>. Previous studies have investigated the relationship between annexin A5 and liver cancer or esophageal cancer and showed that uH2B-related monotone generalization increased the risk of malignant digestive tumors and promoted clinical progression<sup>[31-34]</sup>. This study explored not only the expression of uH2B in colon cancer tissue but also the diagnostic value of its serum level in the diagnosis of colon cancer.

In this study, immunohistochemical staining showed significantly high expression of annexin A5 in colon cancer tissue and demonstrated that the positive expression rate of annexin A5 was significantly higher in patients with lymph node metastasis than in those without. This suggests that annexin A5 may play a role in the promotion of the invasion of lymph nodes by colon cancer cells. Furthermore, approximately 80% of the patients with late-stage (III and IV) colon cancer expressed annexin A5, which was significantly higher than the percentage of patients with stage I or II disease, which suggests that annexin A5 significantly promotes the clinical progression and worsening of colon cancer. Annexin A5 induces the activation of second messengers in cancer cells, which promotes the production of cancer cell differentiation antigens, the proliferation and differentiation of colon cancer cells, and clinical progression.

In conclusion, annexin A5 is highly expressed in serum and tumor tissues of patients with colon cancer, and its expression is closely related to the clinical stage

and presence of lymph node metastasis in patients with colon cancer. Nevertheless, this study has certain limitations. For instance, we did not investigate the relationship between the expression of annexin A5 and the long-term survival of patients with colon cancer.

## COMMENTS

### Background

Colon cancer is a common malignancy of the digestive tract. Studies have shown that the incidence of colon cancer is  $\geq 0.005\%$  and that the incidence has continued to trend upwards in recent years because of risk factors such as diet and smoking.

### Research frontiers

Basic cancer research has shown that changes in the levels of certain molecules affect tumor cell proliferation and differentiation, which in turn affect the development and progression of malignant tumors. Annexin A5 is a glycoprotein that contains a multiplex carboxyl terminus binding domain, which influences the differentiation of surface antigens on cancer cells and promotes tumor proliferation and invasion.

### Innovations and breakthroughs

The objective was to investigate the clinical significance of annexin A5 expression in colon cancer.

### Applications

For patients with colon cancer, annexin A5 expression in cancer tissues is related to lymph node metastasis and tumor grade. Serum level of annexin A5 is related to annexin A5 expression in cancer tissues and is of diagnostic relevance.

### Peer-review

In this study, the authors investigated the expression of annexin A5 in serum and tumor tissues of patients with colon cancer and its clinical significance.

## REFERENCES

- 1 **Chan M**, Hugh-Yeun K, Gresham G, Speers CH, Kennecke HF, Cheung WY. Population-Based Patterns and Factors Associated With Underuse of Palliative Systemic Therapy in Elderly Patients With Metastatic Colon Cancer. *Clin Colorectal Cancer* 2017; **16**: 147-153 [PMID: 27670894 DOI: 10.1016/j.clcc.2016.08.004]
- 2 **Kornmann M**, Formentini A, Ette C, Henne-Bruns D, Kron M, Sander S, Baumann W, Kreuser ED, Staib L, Link KH. Prognostic factors influencing the survival of patients with colon cancer receiving adjuvant 5-FU treatment. *Eur J Surg Oncol* 2008; **34**: 1316-1321 [PMID: 18313881 DOI: 10.1016/j.ejso.2008.01.019]
- 3 **Ueno K**, Hazama S, Mitomori S, Nishioka M, Suehiro Y, Hirata H, Oka M, Imai K, Dahiya R, Hinoda Y. Down-regulation of frizzled-7 expression decreases survival, invasion and metastatic capabilities of colon cancer cells. *Br J Cancer* 2009; **101**: 1374-1381 [PMID: 19773752 DOI: 10.1038/sj.bjc.6605307]
- 4 **Ashktorab H**, Shakoori A, Zarnogi S, Sun X, Varma S, Lee E, Shokrani B, Laiyemo AO, Washington K, Brim H. Reduced Representation Bisulfite Sequencing Determination of Distinctive DNA Hypermethylated Genes in the Progression to Colon Cancer in African Americans. *Gastroenterol Res Pract* 2016; **2016**: 2102674 [PMID: 27688749 DOI: 10.1155/2016/2102674]
- 5 **Bohn M**, Kraus W. [Isolation and characterization of a new placenta specific protein (PP10) (author's transl)]. *Arch Gynecol* 1979; **227**: 125-134 [PMID: 485220 DOI: 10.1007/BF02103286]
- 6 **Boersma HH**, Kietselaer BL, Stolk LM, Bennaghmouch A, Hofstra L, Narula J, Heidendal GA, Reutelingsperger CP. Past, present, and future of annexin A5: from protein discovery to



- clinical applications. *J Nucl Med* 2005; **46**: 2035-2050 [PMID: 16330568]
- 7 **Weixler B**, Warschkow R, Güller U, Zettl A, von Holzen U, Schmied BM, Zuber M. Isolated tumor cells in stage I & II colon cancer patients are associated with significantly worse disease-free and overall survival. *BMC Cancer* 2016; **16**: 106 [PMID: 26879046 DOI: 10.1186/s12885-016-2130-7]
- 8 **Rivera CA**, Ahlberg NC, Taglia L, Kumar M, Blunier A, Benya RV. Expression of GRP and its receptor is associated with improved survival in patients with colon cancer. *Clin Exp Metastasis* 2009; **26**: 663-671 [PMID: 19430935 DOI: 10.1007/s10585-009-9265-8]
- 9 **McArdle CS**, McMillan DC, Hole DJ. The impact of blood loss, obstruction and perforation on survival in patients undergoing curative resection for colon cancer. *Br J Surg* 2006; **93**: 483-488 [PMID: 16555262 DOI: 10.1002/bjs.5269]
- 10 **Mesker WE**, Liefers GJ, Junggeburst JM, van Pelt GW, Alberici P, Kuppen PJ, Miranda NF, van Leeuwen KA, Morreau H, Szuhai K, Tollenaar RA, Tanke HJ. Presence of a high amount of stroma and downregulation of SMAD4 predict for worse survival for stage I-II colon cancer patients. *Cell Oncol* 2009; **31**: 169-178 [PMID: 19478385 DOI: 10.3233/CLO-2009-0478]
- 11 **Grande R**, Corsi D, Mancini R, Gemma D, Ciancola F, Sperduti I, Rossi L, Fabbri A, Diodoro MG, Ruggeri E, Zampa G, Bianchetti S, Gamucci T. Evaluation of relapse-free survival in T3N0 colon cancer: the role of chemotherapy, a multicentric retrospective analysis. *PLoS One* 2013; **8**: e80188 [PMID: 24339871 DOI: 10.1371/journal.pone.0080188]
- 12 **Wang DQ**, Wang K, Yan DW, Liu J, Wang B, Li MX, Wang XW, Liu J, Peng ZH, Li GX, Yu ZH. Ciz1 is a novel predictor of survival in human colon cancer. *Exp Biol Med* (Maywood) 2014; **239**: 862-870 [PMID: 24928862 DOI: 10.1177/1535370213520113]
- 13 **Lederer A**, Herrmann P, Seehofer D, Dietel M, Pratschke J, Schlag P, Stein U. Metastasis-associated in colon cancer 1 is an independent prognostic biomarker for survival in Klatskin tumor patients. *Hepatology* 2015; **62**: 841-850 [PMID: 25953673 DOI: 10.1002/hep.27885]
- 14 **Kazmierczak PM**, Burian E, Eschbach R, Hirner-Eppeneder H, Moser M, Havla L, Eisenblätter M, Reiser MF, Nikolaou K, Cyran CC. Monitoring Cell Death in Regorafenib-Treated Experimental Colon Carcinomas Using Annexin-Based Optical Fluorescence Imaging Validated by Perfusion MRI. *PLoS One* 2015; **10**: e0138452 [PMID: 26393949 DOI: 10.1371/journal.pone.0138452]
- 15 **Chung S**, Gumienny TL, Hengartner MO, Driscoll M. A common set of engulfment genes mediates removal of both apoptotic and necrotic cell corpses in *C. elegans*. *Nat Cell Biol* 2000; **2**: 931-937 [PMID: 11146658 DOI: 10.1038/35046585]
- 16 **Krisko O**, De Ridder L, Cornelissen M. Phosphatidylserine exposure during early primary necrosis (oncosis) in JB6 cells as evidenced by immunogold labeling technique. *Apoptosis* 2004; **9**: 495-500 [PMID: 15192332 DOI: 10.1023/B:APPT.0000031452.75162.75]
- 17 **Holler N**, Zaru R, Micheau O, Thome M, Attinger A, Valitutti S, Bodmer JL, Schneider P, Seed B, Tschopp J. Fas triggers an alternative, caspase-8-independent cell death pathway using the kinase RIP as effector molecule. *Nat Immunol* 2000; **1**: 489-495 [PMID: 11101870 DOI: 10.1038/82732]
- 18 **Reutelingsperger CP**, Hornstra G, Hemker HC. Isolation and partial purification of a novel anticoagulant from arteries of human umbilical cord. *Eur J Biochem* 1985; **151**: 625-629 [PMID: 3896792 DOI: 10.1111/j.1432-1033.1985.tb09150.x]
- 19 **Demange P**, Voges D, Benz J, Liemann S, Göttig P, Berendes R, Burger A, Huber R. Annexin V: the key to understanding ion selectivity and voltage regulation? *Trends Biochem Sci* 1994; **19**: 272-276 [PMID: 7519374 DOI: 10.1016/0968-0004(94)90002-7]
- 20 **Corsten MF**, Hofstra L, Narula J, Reutelingsperger CP. Counting heads in the war against cancer: defining the role of annexin A5 imaging in cancer treatment and surveillance. *Cancer Res* 2006; **66**: 1255-1260 [PMID: 16452175 DOI: 10.1158/0008-5472.CAN-05-3000]
- 21 **Park N**, Chun YJ. Auranofin promotes mitochondrial apoptosis by inducing annexin A5 expression and translocation in human prostate cancer cells. *J Toxicol Environ Health A* 2014; **77**: 1467-1476 [PMID: 25343295 DOI: 10.1080/15287394.2014.955834]
- 22 **Hong M**, Park N, Chun YJ. Role of annexin a5 on mitochondria-dependent apoptosis induced by tetramethoxystilbene in human breast cancer cells. *Biomol Ther* (Seoul) 2014; **22**: 519-524 [PMID: 25489419 DOI: 10.4062/biomolther.2014.112]
- 23 **Vangestel C**, Van de Wiele C, Mees G, Mertens K, Staelens S, Reutelingsperger C, Pauwels P, Van Damme N, Peeters M. Single-photon emission computed tomographic imaging of the early time course of therapy-induced cell death using technetium 99m tricarbonyl His-annexin A5 in a colorectal cancer xenograft model. *Mol Imaging* 2012; **11**: 135-147 [PMID: 22469241]
- 24 **Shin DW**, Kwon YJ, Ye DJ, Baek HS, Lee JE, Chun YJ. Auranofin Suppresses Plasminogen Activator Inhibitor-2 Expression through Annexin A5 Induction in Human Prostate Cancer Cells. *Biomol Ther* (Seoul) 2017; **25**: 177-185 [PMID: 27956714 DOI: 10.4062/biomolther.2016.223]
- 25 **Deng S**, Wang J, Hou L, Li J, Chen G, Jing B, Zhang X, Yang Z. Annexin A1, A2, A4 and A5 play important roles in breast cancer, pancreatic cancer and laryngeal carcinoma, alone and/or synergistically. *Oncol Lett* 2013; **5**: 107-112 [PMID: 23255903 DOI: 10.3892/ol.2012.959]
- 26 **Schaper FL**, Reutelingsperger CP. 99mTc-HYNIC-Annexin A5 in Oncology: Evaluating Efficacy of Anti-Cancer Therapies. *Cancers* (Basel) 2013; **5**: 550-568 [PMID: 24216991 DOI: 10.3390/cancers5020550]
- 27 **Kwon YJ**, Jung JJ, Park NH, Ye DJ, Kim D, Moon A, Chun YJ. Annexin a5 as a new potential biomarker for Cisplatin-induced toxicity in human kidney epithelial cells. *Biomol Ther* (Seoul) 2013; **21**: 190-195 [PMID: 24265863 DOI: 10.4062/biomolther.2013.026]
- 28 **Jeong JJ**, Park N, Kwon YJ, Ye DJ, Moon A, Chun YJ. Role of annexin A5 in cisplatin-induced toxicity in renal cells: molecular mechanism of apoptosis. *J Biol Chem* 2014; **289**: 2469-2481 [PMID: 24318879 DOI: 10.1074/jbc.M113.450163]
- 29 **Tsukamoto H**, Tanida S, Ozeki K, Ebi M, Mizoshita T, Shimura T, Mori Y, Kataoka H, Kamiya T, Fukuda S, Higashiyama S, Joh T. Annexin A2 regulates a disintegrin and metalloproteinase 17-mediated ectodomain shedding of pro-tumor necrosis factor- $\alpha$  in monocytes and colon epithelial cells. *Inflamm Bowel Dis* 2013; **19**: 1365-1373 [PMID: 23702712 DOI: 10.1097/MIB.0b013e318281f43a]
- 30 **Tristante E**, Martínez CM, Jiménez S, Mora L, Carballo F, Martínez-Lacaci I, de Torre-Mingueta C. Association of a characteristic membrane pattern of annexin A2 with high invasiveness and nodal status in colon adenocarcinoma. *Transl Res* 2015; **166**: 196-206 [PMID: 25795236 DOI: 10.1016/j.trsl.2015.02.006]
- 31 **Schurgers LJ**, Burgmaier M, Ueland T, Schutters K, Aakhus S, Hofstra L, Gullestad L, Aukrust P, Hellmich M, Narula J, Reutelingsperger CP. Circulating annexin A5 predicts mortality in patients with heart failure. *J Intern Med* 2016; **279**: 89-97 [PMID: 26223343 DOI: 10.1111/joim.12396]
- 32 **Ogawa K**, Ohtsuki K, Shibata T, Aoki M, Nakayama M, Kitamura Y, Ono M, Ueda M, Doue T, Onoguchi M, Shiba K, Odani A. Development and evaluation of a novel (99m)tc-labeled annexin A5 for early detection of response to chemotherapy. *PLoS One* 2013; **8**: e81191 [PMID: 24324676 DOI: 10.1371/journal.pone.0081191]
- 33 **Paweletz CP**, Ornstein DK, Roth MJ, Bichsel VE, Gillespie JW, Calvert VS, Vocke CD, Hewitt SM, Duray PH, Herring J, Wang QH, Hu N, Linehan WM, Taylor PR, Liotta LA, Emmert-Buck MR, Petricoin EF 3rd. Loss of annexin 1 correlates with early onset of tumorigenesis in esophageal and prostate carcinoma. *Cancer Res* 2000; **60**: 6293-6297 [PMID: 11103786]
- 34 **Zaidi AH**, Gopalakrishnan V, Kasi PM, Zeng X, Malhotra U,

Balasubramanian J, Visweswaran S, Sun M, Flint MS, Davison JM, Hood BL, Conrads TP, Bergman JJ, Bigbee WL, Jobe BA. Evaluation of a 4-protein serum biomarker panel-biglycan,

annexin-A6, myeloperoxidase, and protein S100-A9 (B-AMP)-for the detection of esophageal adenocarcinoma. *Cancer* 2014; **120**: 3902-3913 [PMID: 25100294 DOI: 10.1002/cncr.28963]

**P- Reviewer:** Faerch K, Gordon LG **S- Editor:** Qi Y  
**L- Editor:** Wang TQ **E- Editor:** Huang Y





Published by **Baishideng Publishing Group Inc**  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-223-8242  
Fax: +1-925-223-8243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045