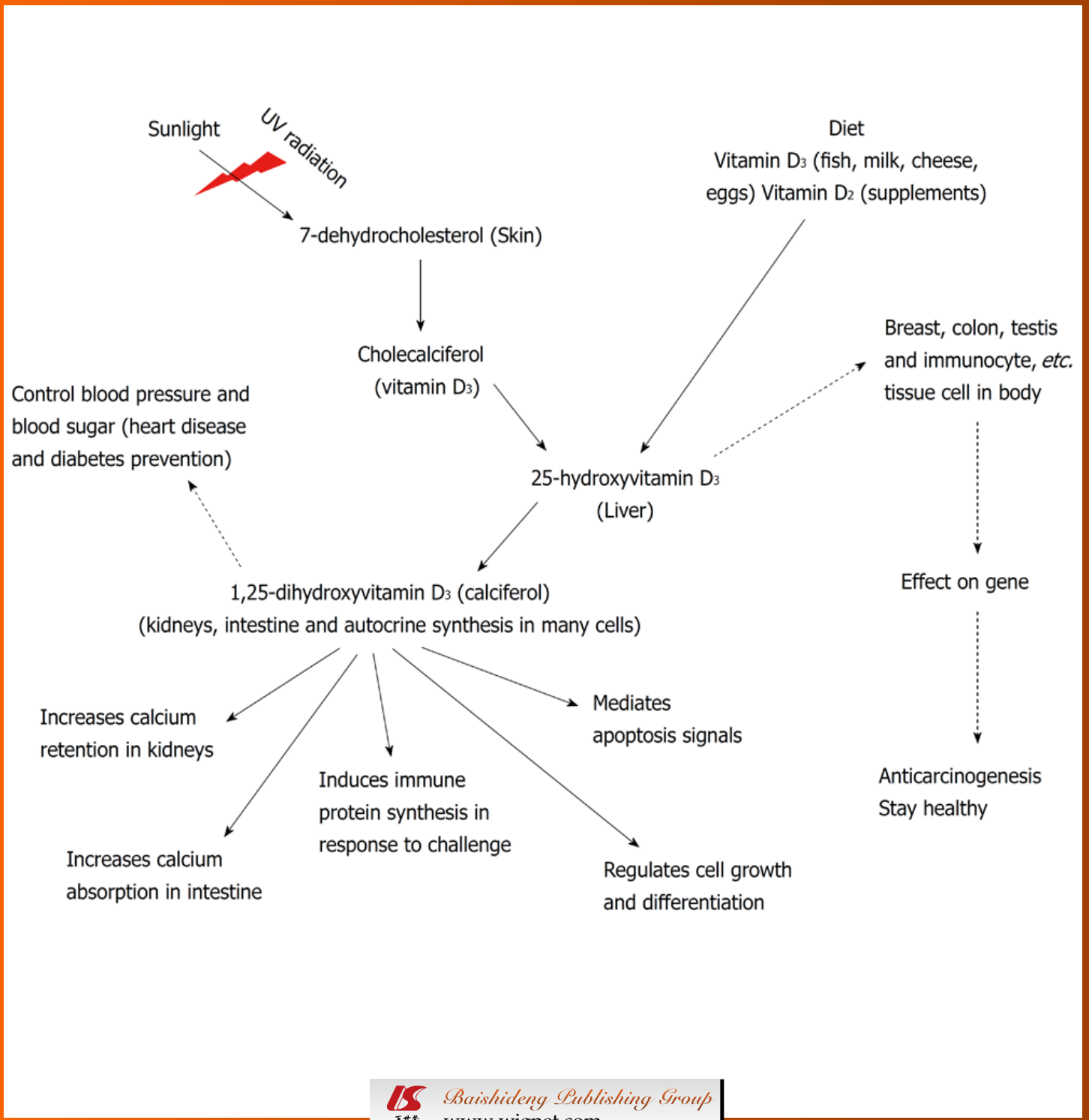
ISSN 1948-5204 (online)

World Journal of *Gastrointestinal Oncology*

World J Gastrointest Oncol 2011 August 15; 3(8): 119-127



Baishideng Publishing Group
www.wjgnet.com

WJGO World Journal of Gastrointestinal Oncology

A peer-reviewed, online, open-access journal of gastrointestinal oncology

Editorial Board

2009-2013

The *World Journal of Gastrointestinal Oncology* Editorial Board consists of 404 members, representing a team of worldwide experts in gastrointestinal oncology. They are from 41 countries, including Argentina (1), Australia (9), Austria (1), Belgium (4), Brazil (2), Bulgaria (1), Canada (4), Chile (2), China (51), Czech Republic (1), Finland (3), France (5), Germany (18), Greece (12), Hungary (2), India (9), Iran (3), Ireland (2), Israel (4), Italy (34), Japan (47), Kuwait (2), Mexico (1), Netherlands (8), New Zealand (2), Norway (1), Poland (4), Portugal (5), Romania (1), Saudi Arabia (1), Serbia (2), Singapore (4), South Korea (27), Spain (11), Sweden (6), Switzerland (2), Syria (1), Thailand (1), Turkey (6), United Kingdom (13), and United States (91).

Guo-Qiang Xu, *Hangzhou*
Winnie Yeo, *Hong Kong*
Ying-Yan Yu, *Shanghai*
Siu Tsan Yuen, *Hong Kong*
Wei-Hui Zhang, *Harbin*
Li Zhou, *Beijing*
Yong-Ning Zhou, *Lanzhou*

Czech Republic

Ondrej Slaby, *Brno*

Finland

Riyad Bendardaf, *Turku*
Pentti Ilmari Sipponen, *Helsinki*
Markku Voutilainen, *Jyväskylä*

France

Bouvier Anne-Marie, *Cedex*
Stéphane Benoist, *Boulogne*
Ouaissi Mehdi, *Cedex*
Isabelle V Seuningen, *Cedex*
Karem Slim, *Clermont-Ferrand*

Germany

Han-Xiang An, *Marburg*
Karl-Friedrich Becker, *München*
Stefan Boeck, *Munich*
Dietrich Doll, *Marburg*
Volker Ellenrieder, *Marburg*
Joachim P Fannschmidt, *Heidelberg*
Ines Gütgemann, *Bonn*
Jakob R Izbicki, *Hamburg*
Gisela Keller, *München*
Jörg H Kleeff, *Munich*
Axel Kleespies, *Munich*
Hans-Joachim Meyer, *Solingen*
Lars Mueller, *Kiel*
Marc A Reymond, *Bielefeld*
Robert Rosenberg, *München*
Oliver Stoeltzing, *Mainz*
Ludwig G Strauss, *Heidelberg*

Greece

Ekaterini Chatzaki, *Alexandroupolis*
Eelco de Bree, *Heraklion*
Maria Gazouli, *Athens*
Vassilis Georgoulias, *Crete*
John Griniatsos, *Athens*
Ioannis D Kanellos, *Thessaloniki*
Vaios Karanikas, *Larissa*
Georgios Koukourakis, *Athens*
Gregory Kouraklis, *Athens*
Dimitrios H Roukos, *Ioannina*
Konstantinos Nik Syrigos, *Athens*
Ioannis A Voutsadakis, *Larissa*

Hungary

László Herszényi, *Budapest*
Zsuzsa Schaff, *Budapest*

India

Uday Chand Ghoshal, *Lucknow*
Ruchika Gupta, *New Delhi*
Kalpesh Jani, *Gujarat*
Ashwani Koul, *Chandigarh*
Balraj Mittal, *Lucknow*
Rama Devi Mittal, *Lucknow*
Susanta Roychoudhury, *Kolkata*
Yogeshwer Shukla, *Lucknow*
Imtiaz Ahmed Wani, *Kashmir*

Iran

Mohammad R Abbaszadegan, *Mashhad*
Reza Malekezdeh, *Tehran*
Mohamad A Pourhoseingholi, *Tehran*

Ireland

Aileen Maria Houston, *Cork*
Colm Ó'Moráin, *Dublin*

Israel

Nadir Arber, *Tel Aviv*
Dan David Hershko, *Haifa*
Eytan Domany, *Rehovot*
Yaron Niv, *Patch Tikva*

Italy

Massimo Aglietta, *Turin*
Azzariti Amalia, *Bari*
Domenico Alvaro, *Rome*
Marco Braga, *Milan*
Federico Cappuzzo, *Rozzano*
Fabio Carboni, *Rome*
Vincenzo Cardinale, *Rome*
Luigi Cavanna, *Piacenza*
Riccardo Dolcetti, *Aviano*
Pier Francesco Ferrucci, *Milano*
Francesco Fiorica, *Ferrara*
Gennaro Galizia, *Naples*
Silvano Gallus, *Milan*
Milena Gusella, *Trecenta*
Roberto F Labianca, *Bergamo*
Massimo Libra, *Catania*
Roberto Manfredi, *Bologna*
Gabriele Masselli, *Roma*
Simone Mocellin, *Padova*
Gianni Mura, *Arezzo*
Gerardo Nardonen, *Napoli*
Francesco Perri, *San Benedetto del Tronto*
Francesco Recchia, *Avezzano*
Vittorio Ricci, *Pavia*
Fabrizio Romano, *Monza*
Antonio Russo, *Palermo*
Daniele Santini, *Roma*
Claudio Sorio, *Verona*
Cosimo Sperti, *Padova*
Gianni Testino, *Genova*
Giuseppe Tonini, *Rome*
Bruno Vincenzi, *Rome*
Angelo Zullo, *Rome*

Japan

Keishiro Aoyagi, *Kurume*
Suminori Akiba, *Kagoshima*
Narikazu Boku, *Shizuoka*
Yataro Daigo, *Tokyo*
Itaru Endo, *Yokohama*
Mitsuhiro Fujishiro, *Tokyo*
Osamu Handa, *Kyoto*
Kenji Hibi, *Yokohama*
Asahi Hishida, *Nagoya*
Eiso Hiyama, *Hiroshima*
Atsushi Imagawa, *Okayama*
Johji Inazawa, *Tokyo*
Terumi Kamisawa, *Tokyo*
Tatsuo Kanda, *Niigata*
Masaru Katoh, *Tokyo*
Takayoshi Kiba, *Hyogo*
Hajime Kubo, *Kyoto*
Yukinori Kurokawa, *Osaka*
Chihaya Maesawa, *Morioka*
Yoshinori Marunaka, *Kyoto*
Hishairo Matsubara, *Chiba*
Osam Mazda, *Kyoto*
Shinichi Miyagawa, *Matsumoto*
Eiji Miyoshi, *Suita*
Toshiyuki Nakayama, *Nagasaki*
Masahiko Nishiyama, *Saitama*
Koji Oba, *Kyoto*
Masayuki Ohtsukam, *Chiba*
Masao Seto, *Aichi*
Tomoyuki Shibata, *Aichi*
Mitsugi Shimoda, *Tochigi*
Haruhiko Sugimura, *Hamamatsu*
Tomomitsu Tahara, *Aichi*
Shinji Takai, *Osaka*
Satoru Takayama, *Nagoya*
Hiroya Takiuchi, *Osaka*
Akio Tomoda, *Tokyo*
Akihiko Tsuchida, *Tokyo*
Yasuo Tsuchiya, *Niigata*
Takuya Watanabe, *Niigata*
Toshiaki Watanabe, *Tokyo*
Hiroshi Yasuda, *Kanagawa*
Yo-ichi Yamashita, *Hiroshima*
Hiroki Yamaue, *Wakayama*
Hiroshi Yokomizo, *Kumamoto*
Yutaka Yonemura, *Osaka*
Reigetsu Yoshikawa, *Hyogo*

Kuwait

Fahd Al-Mulla, *Safat*
Salem Alshemmari, *Safat*

Mexico

Oscar GA Rodriguez, *Mexico*

Netherlands

Jan Paul De Boer, *Amsterdam*
Bloemena Elisabeth, *Amsterdam*
Peter JK Kuppen, *Leiden*
Gerrit Albert Meijer, *Hattem*
Anya N Milne, *Utrecht*
Godefridus J Peters, *Amsterdam*
Cornelis FM Sier, *Leiden*
Peter Derk Siersema, *Utrecht*

New Zealand

Lynnette R Ferguson, *Auckland*
Jonathan Barnes Koea, *Auckland*

Norway

Kjetil Søreide, *Stavanger*

Poland

Barbara W Chwirot, *Torun*
Andrzej Szkaradkiewicz, *Poznan*
Michal Tenderenda, *Polskiego*
Jerzy Wydmański, Gliwice

Portugal

Maria FRM Gartner, *Porto*
Suriano Gianpaolo, *Porto*
Celso A Reis, *Porto*
Lucio Lara Santos, *Porto*
Maria Raquel Campos Seruca, *Porto*

Romania

Marius Raica, *Timisoara*

Saudi Arabia

Ragab Hani Donkol, *Abha*

Serbia

Milos M Bjelovic, *Belgrade*
Goran Stanojevic, *Nis*

Singapore

Peh Yean Cheah, *Singapore*
Si-Shen Feng, *Singapore*
Zhi-Wei Huang, *Singapore*
Qi Zeng, *Singapore*

South Korea

Seungmin Bang, *Seoul*
Daeho Cho, *Seoul*
Byung Ihn Choi, *Seoul*
Hyun Cheol Chung, *Seoul*
Dietrich Doll, *Seoul*
Sang-Uk Han, *Suwon*
Jun-Hyeog Jang, *Incheon*
Seong Woo Jeon, *Daegu*
Dae H Kang, *Mulgeum-Gigu*
Gyeong H Kang, *Seoul*
Dong Yi Kim, *Gwangju*
Jae J Kim, *Seoul*
Jin Cheon Kim, *Seoul*
Jong Gwang Kim, *Daegu*
Min Chan Kim, *Busan*
Samyong Kim, *Daejeon*
Jung Weon Lee, *Seoul*
Kyu Taek Lee, *Seoul*
Kyung Hee Lee, *Daegu*
Na Gyong Lee, *Seoul*
Suk Kyeong Lee, *Seoul*
Jong-Baeck Lim, *Seoul*
Young Joo Min, *Ulsan*
Sung-Soo Park, *Seoul*
Young Kee Shin, *Seoul*
Hee Jung Son, *Seoul*
Si Young Song, *Seoul*

Spain

Manuel Benito, *Madrid*
Ignacio Casal, *Madrid*
Antoni Castells, *Catalonia*
Laura Elnitski, *Barcelona*
Jose JG Marin, *Salamanca*
Joan Maurel, *Barcelona*
Emma Folch Puy, *Barcelona*
Jose Manuel Ramia, *Guadalajara*
Margarita Sanchez-Beato, *Madrid*
Laura Valle, *Barcelona*
Jesus Vioque, *San Juan de Alicante*

Sweden

Nils Albiin, *Stockholm*
Samuel Lundin, *Göteborg*
Haile Mahteme, *Uppsala*
Richard Palmqvist, *Umeå*
Marianne Quiding-Järbrink, *Göteborg*
Ning Xu, *Lund*

Switzerland

Paul M Schneider, *Zürich*
Luigi Tornillo, *Schönbeinstrasse*

Syria

Zuhir Alshehabi, *Lattakia*

Thailand

Sopit Wongkham, *Khon Kaen*

Turkey

Uğur Coşkun, *Ankara*
Vedat Goral, *Diyarbakir*
Sukru M Erturk, *Istanbul*
RP Tez Mesut, *Ankara*
Yavuz Selim Sari, *Istanbul*
Murat H Yener, *Istanbul*

United Kingdom

Runjan Chetty, *Scotland*
Chris Deans, *Edinburgh*
Dipok Kumar Dhar, *London*
Thomas RJ Evans, *Glasgow*
Giuseppe Garcea, *Leicester*
Oleg Gerasimenko, *Liverpool*
Neena Kalia, *Birmingham*
Anthony Maraveyas, *East Yorkshire*
Andrew Maw, *North Wales*
Kymberley Thorne, *Swansea*
Chris Tselepis, *Birmingham*
Ling-Sen Wong, *Coventry*
Lu-Gang Yu, *Liverpool*

United States

Gianfranco Alpini, *Temple*
Seung J Baek, *Knoxville*
Jamie S Barkin, *Miami Beach*
Carol Bernstein, *Arizona*
Paolo Boffetta, *New York*
Kimberly M Brown, *Kansas*
De-Liang Cao, *Springfield*
Wei-Biao Cao, *Providence*
Chris N Conteas, *Los Angeles*
Joseph J Cullen, *Iowa*
James C Cusack, *Massachusetts*
Ananya Das, *Scottsdale*
Juan Dominguez-Bendala, *Miami*
Wafik S El-Deiry, *Philadelphia*
Guy D Eslick, *Boston*
Thomas J Fahey III, *New York*
James W Freeman, *San Antonio*
Bruce J Giantonio, *Philadelphia*
Ajay Goel, *Dallas*
Karen Gould, *Omaha*
Nagana GA Gowda, *West Lafayette*
Stephen R Grobmyer, *Florida*
Paul J Higgins, *New York*
Young S Hahn, *Charlottesville*
Shou-Wei Han, *Georgia*
John W Harmon, *Maryland*
Steven N Hochwald, *Gainesville*
Jason L Hornick, *Boston*
Qin Huang, *Duarte*
Su-Yun Huang, *Houston*
Jamal A Ibdah, *Columbia*
Yihong JC Kaufmann, *Little Rock*
Temitope O Keku, *Chapel Hill*
Saeed Khan, *Silver Spring*
Peter S Kozuch, *New York*
Sunil Krishnan, *Houston*
Robert R Langley, *Houston*
Feng-Zhi Li, *Carlton*
Otto Schiueh-Tzang Lin, *Seattle*
Ke-Bin Liu, *Augusta*
Rui-Hai Liu, *Ithaca*
Xiang-Dong Liu, *Wilmington*
Deryk Thomas Loo, *San Francisco*
Andrew M Lowy, *La Jolla*
Bo Lu, *Nashville*
David M Lubman, *Ann Arbor*
Ju-Hua Luo, *Morgantown*
James D Luketich, *Pittsburgh*
Henry T Lynch, *Omaha*
Shelli R Mcalpine, *San Diego*
Anil Mishra, *Cincinnati*
Priyabrata Mukherjee, *Rochester*
Steffan T Nawrocki, *San Antonio*
Shuji Ogino, *Boston*
Macaulay Onuigbo, *Eau Claire*
Jong Park, *Tampa*
Philip Agop Philip, *Detriot*
Iryna V Pinchuk, *Galveston*
Blase N Polite, *Chicago*
James A Radosevich, *Chicago*
Jasti S Rao, *Peoria*
Srinevas K Reddy, *Durham*
Raffaniello Robert, *New York*
Stephen H Safe, *College Station*
Muhammad W Saif, *New Haven*
Prateek Sharma, *Kansas*
Eric Tatsuo Shinohara, *Philadelphia*
Liviu A Sicinschi, *Nashville*
William Small Jr, *Chicago*
Sanjay K Srivastava, *Amarillo*
Gloria H Su, *New York*
Sujha Subramanian, *Waltham*
Mitsushige Sugimoto, *Houston*
David W Townsend, *Knoxville*
Asad Umar, *Rockville*
Ji-Ping Wang, *Buffalo*
Zheng-He Wang, *Cleveland*
Michael J Wargovich, *Charleston*
Neal W Wilkinson, *Iowa*
Siu-Fun Wong, *Pomona*
Shen-Hong Wu, *New York*
Jing-Wu Xie, *Indianapolis*
Ke-Ping Xie, *Houston*
Hao-Dong Xu, *Rochester*
Xiao-Chun Xu, *Houston*
Yoshio Yamaoka, *Houston*
Gary Y Yang, *Buffalo*
Wan-Cai Yang, *Chicago*
Zeng-Quan Yang, *Detroit*
Zuo-Feng Zhang, *Los Angeles*

WJGO
World Journal of Gastrointestinal Oncology

Contents

Monthly Volume 3 Number 8 August 15, 2011

World Journal of Gastrointestinal Oncology
Volume 3 Number 8 August 15, 2011

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Oncology

LAUNCH DATE
October 15, 2009

SPONSOR
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

EDITING
Editorial Board of *World Journal of Gastrointestinal Oncology*,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1891
Fax: +86-10-8538-1893
E-mail: wjgo@wjgnet.com
http://www.wjgnet.com

PUBLISHING
Baishideng Publishing Group Co., Limited,
Room 1701, 17/F, Henan Bulding,
No.90 Jaffe Road, Wanchai,
Hong Kong, China
Fax: +852-3115-8812
Telephone: +852-5804-2046
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

SUBSCRIPTION
Beijing Baishideng BioMed Scientific Co., Ltd.,
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
http://www.wjgnet.com

ONLINE SUBSCRIPTION
One-Year Price 216.00 USD

PUBLICATION DATE
August 15, 2011

ISSN
ISSN 1948-5204 (online)

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Journal of Gastrointestinal Oncology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1891
Fax: +86-10-8538-1893
E-mail: wjgo@wjgnet.com
http://www.wjgnet.com

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/1948-5204/g_info_20100312180518.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/1948-5204office

World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v3.i8.119

World J Gastrointest Oncol 2011 August 15; 3(8): 119-122
ISSN 1948-5204 (online)

EDITORIAL

Intracellular chloride regulates the G1/S cell cycle progression in gastric cancer cells

Atsushi Shiozaki, Eigo Otsuji, Yoshinori Marunaka

Atsushi Shiozaki, Eigo Otsuji, Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, Kyoto 602-8566, Japan
Yoshinori Marunaka, Department of Molecular Cell Physiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, 602-8566, Japan; Japan Institute for Food Education and Health, St. Agnes' University, Kyoto 602-8013, Japan
Author contributions: Shiozaki A carried out the experiments for this review and wrote the manuscript; Otsuji E supervised the research; Marunaka Y designed the experiments and supervised the research.
Correspondence to: Dr. Atsushi Shiozaki, Assistant Professor, Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan. shiozaki@koto.kpu-m.ac.jp
Telephone: +81-75-2515527 Fax: +81-75-2515522
Received: March 31, 2011 Revised: July 25, 2011
Accepted: August 1, 2011
Published online: August 15, 2011

Abstract

Recent studies show that ion channels/transporters play important roles in fundamental cellular functions. Several reports indicating the important roles of Cl^- channels/transporters on cell proliferation suggest that the intracellular chloride concentration ($[Cl^-]_i$) regulated by them would be one of critical messengers. We investigated whether the $[Cl^-]_i$ controls cell proliferation and cell cycle progression in human gastric cancer cells. Our studies indicated that furosemide, a blocker of $Na^+/K^+/2Cl^-$ cotransporter (NKCC), diminished cell growth by delaying the G_1-S phase progression in gastric cancer cells with high expression and activity of NKCC. Furthermore, we found that the culture in the low Cl^- medium (replacement of Cl^- by NO_3^-) decreased the $[Cl^-]_i$ and inhibited cell growth of gastric cancer cells and that this inhibition of cell growth was due to cell cycle arrest at the G_0/G_1 phase caused by diminution of CDK2 and phosphorylated Rb. The culture of cells in the low Cl^- medium significantly increased expressions of p21 mRNA and protein. In addition, the low Cl^- medium induced phosphorylation of mitogen activated protein kinases (MAPKs). Treatment with an inhibitor of p38 or JNK significantly suppressed p21 upregulation caused by culture in a low Cl^- medium and rescued gastric cancer cells from the low Cl^--induced G_1 cell cycle arrest. These findings revealed that the $[Cl^-]_i$ affects the cell proliferation *via* activation of MAPKs through upregulation of p21 in gastric cancer cells. Our results suggest that the $[Cl^-]_i$ regulates important cellular functions in gastric cancer cells, leading to the development of novel therapeutic strategies.

Key words: Intracellular chloride; Cell proliferation; Cell cycle; Gastric cancer; Cl^- channel; Cl^- transporter

Peer reviewer: Barbara W Chwirot, Professor, Department of Medical Biology, Institute of General and Molecular Biology, Nicolaus Copernicus University, Gagarina 9, Torun 87-100, Poland

Shiozaki A, Otsuji E, Marunaka Y. Intracellular chloride regulates the G_1/S cell cycle progression in gastric cancer cells. *World J Gastrointest Oncol* 2011; 3(8): 119-122 Available from: URL: http://www.wjgnet.com/1948-5204/full/v3/i8/119.htm DOI: http://dx.doi.org/10.4251/wjgo.v3.i8.119

INTRODUCTION

Over the past two decades, many researchers have reported that ion channels and transporters play important roles in fundamental cellular functions. Particularly, their physiological roles in cell proliferation have been considered since cell volume changes, which require the participation of ion movement across the cell membrane,

are indispensable in cell cycle progression. Recently, the roles of ion transporters have been studied in cancer cells[1-3] and various types of ion transporters have been found in cancers of digestive organs. Some types of K^+ channels, such as voltage-gated Kv1.3 channel, voltage-gated HERG channel and KCNK9 channel, have been reported to be expressed at extremely higher levels in colonic carcinoma specimens than in normal colon tissues[4-6]. In gastric cancer, the voltage-gated HERG channel has revealed cancer-limited expression and its blocker diminishes the G_1 to S phase transition[7]. Furthermore, increased mRNA levels of voltage-gated Cav1.2 Ca^{2+} channels and Ca^{2+}-conducting channels (TRPM8) have been reported in colorectal adenocarcinoma[8,9].

Several reports indicate that Cl^- channels/transporters play an important role in gastrointestinal cancer cells. For instance, transcriptional downregulation of Ca^{2+}-activated $2Cl^-$ channels (CLCA1 and CLCA2) genes is detected in colorectal tumor samples[10]. Sarosi *et al*[11] have reported that the Cl^-/HCO_3^- exchanger influences the proliferation of Barrett's esophageal adenocarcinoma cells through changes of intracellular pH. In addition, we previously found that mRNA and the functional expression levels of $Na^+/K^+/2Cl^-$ cotransporter (NKCC) were higher in poorly-differentiated type gastric adenocarcinoma cells than in differentiated cells[12]. These reports indicate that the transepithelial Cl^- transport plays an important role in cell proliferation of gastrointestinal cancer cells. From this viewpoint, we investigated whether the intracellular chloride concentration ($[Cl^-]_i$) regulates cell proliferation and cell cycle progression in human gastric cancer cells.

INTRACELLULAR CHLORIDE AND SIGNAL TRANSDUCTION

Our study[13] indicates that the intracellular chloride could act as a signal to regulate mRNA expression of ion channel in renal epithelial A6 cells, suggesting that many physiological functions are associated with the change of the $[Cl^-]_i$. Similarly, Heimlich *et al*[14] have shown that an alteration of the $[Cl^-]_i$ plays an important role in the activation of signaling molecules upstream of the mitochondria, specifically impairing the intrinsic apoptotic pathway. In a mouse macula densa cell line, low chloride stimulates prostaglandin E2 release and COX-2 expression through activation of mitogen activated protein kinases (MAPKs)[15]. These reports suggest that the changes in the $[Cl^-]_i$ might act as a regulator of various types of intracellular enzymes. We previously showed that furosemide, a blocker of NKCC, diminished cell growth by delaying the G_1-S phase progression in gastric cancer cells with high expression and activity of NKCC[12] (Figure 1). NKCC is one of the important transporters controlling the $[Cl^-]_i$ *via* uptake of Cl^- into the intracellular space and, therefore, furosemide decreases the $[Cl^-]_i$[16] (Figure 1). Based on these findings, we hypothesized that the $[Cl^-]_i$ would be one of critical messengers regulating cell proliferation and investigated whether the $[Cl^-]_i$ regulates cell cycle progression in human gastric cancer cells.

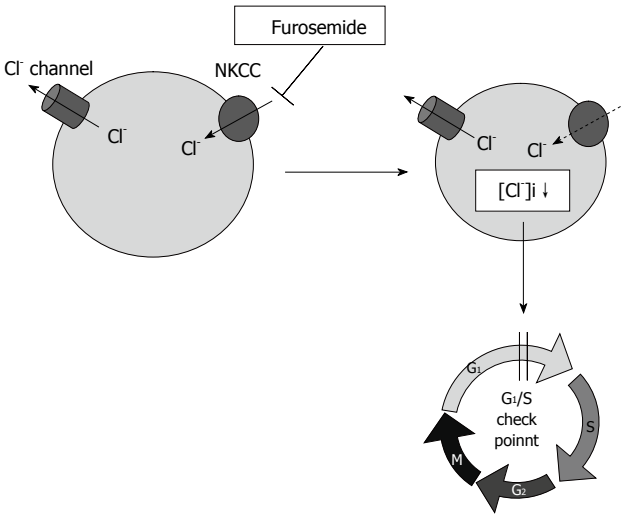


Figure 1 $Na^+/K^+/2Cl^-$ cotransporter controls the intracellular chloride concentration *via* uptake of Cl^- into the intracellular space. Furosemide, a blocker of $Na^+/K^+/2Cl^-$ cotransporter, delays the G_1-S phase progression by decreasing the intracellular chloride concentration ($[Cl^-]_i$) in gastric cancer cells.

CELL CYCLE PROGRESSION AND $[Cl^-]_i$ IN GASTRIC CANCER CELLS

We directed our interest to the roles of the $[Cl^-]_i$ in cell proliferation and cell cycle progression of gastric cancer cells. We applied media containing various chloride concentrations to human gastric cancer MKN28 cells and measured the $[Cl^-]_i$ at 48 h after the application. The $[Cl^-]_i$ of gastric cancer cells incubated in the normal medium was around 30 mmol/L. When cells were incubated in the low Cl^- medium (replacement of Cl^- by NO_3^-) for 48 h, the $[Cl^-]_i$ decreased to around 0 mmol/L. Furthermore, the $[Cl^-]_i$ of cells cultured in the media containing various chloride concentrations was proportionally dependent on the chloride concentration of the cultured medium[17,18]. These findings indicated that our experimental system using the low Cl^- medium can be used as a model of the $[Cl^-]_i$ regulation (Figure 2). The proliferation rate in MKN28 cells was significantly diminished by the culture in the low Cl^- medium compared with that in a normal one. In addition, analysis of cell proliferation of MKN28 cells cultured in the media containing various chloride concentrations indicated that the rate of cell proliferation depends on the extracellular chloride concentration[18]. These results revealed that the $[Cl^-]_i$ plays a key role in proliferation of gastric cancer cells. Cell cycle analysis revealed that the population of MKN28 cells staying in the G_0/G_1 phase was significantly increased and that cells staying in the S or G_2/M phase were reduced by the culture in the low Cl^- medium, suggesting that the decrease of the $[Cl^-]_i$ shows an inhibitory effect on the proliferation of gastric cancer cells by mainly diminishing the transition from the G_1 phase to the S phase[18] (Figure 3).

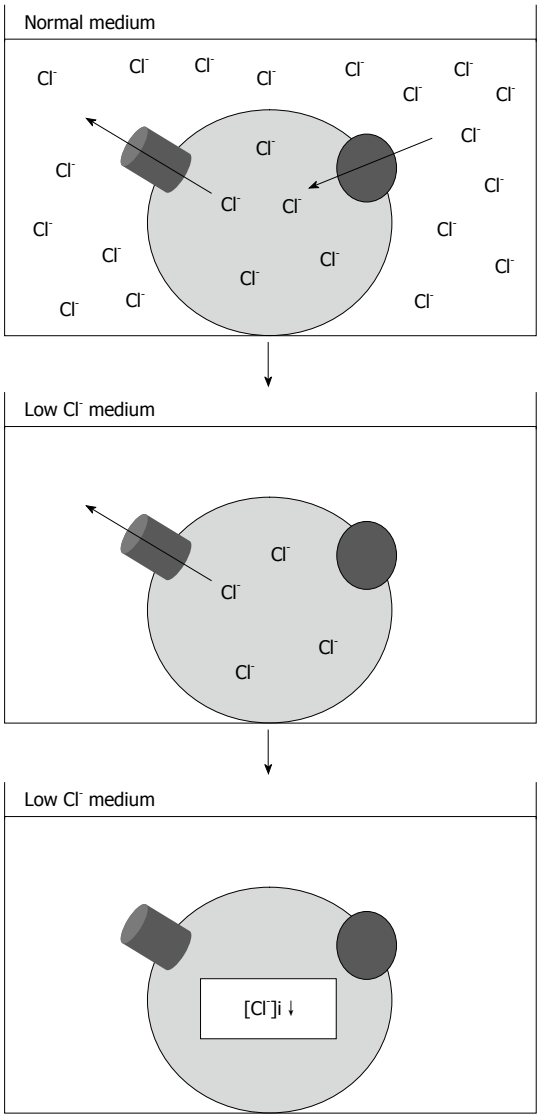


Figure 2 Experimental method for regulation of the intracellular chloride concentration of cultured cells. The intracellular chloride concentration ($[Cl^-]_i$) of gastric cancer cells is decreased by the culture in the low Cl^- medium, which were prepared by substituting, respectively, NaCl and KCl with $NaNO_3$ and KNO_3.

$[Cl^-]_i$ CONTROLS THE G_1/S CELL CYCLE CHECK POINT BY REGULATING THE EXPRESSION OF p21 IN GASTRIC CANCER CELLS

We analyzed the expression of cell cycle-associated proteins involved in G_1-S phase transition to determine the mechanisms by which the decrease of the $[Cl^-]_i$ inhibited the proliferation of MKN28 cells. The culture in the low Cl^- medium significantly decreased phosphorylation of Rb. The expression of CDK2 protein, which is located at upstream of Rb in a signal pathway, was significantly downregulated by the culture in the low Cl^- medium. Furthermore, the low Cl^- medium elevated expression of p21[18]. These results suggest that the $[Cl^-]_i$ of gastric cancer cells acts on the transition from the G_1 phase to the S phase by regulating the expression of p21 and its downstream proteins in signal pathways (Figure 3). We found similar effects of the $[Cl^-]_i$ on cell cycle associated proteins in human prostatic cancer cells and mouse osteoblast cells[16,19].

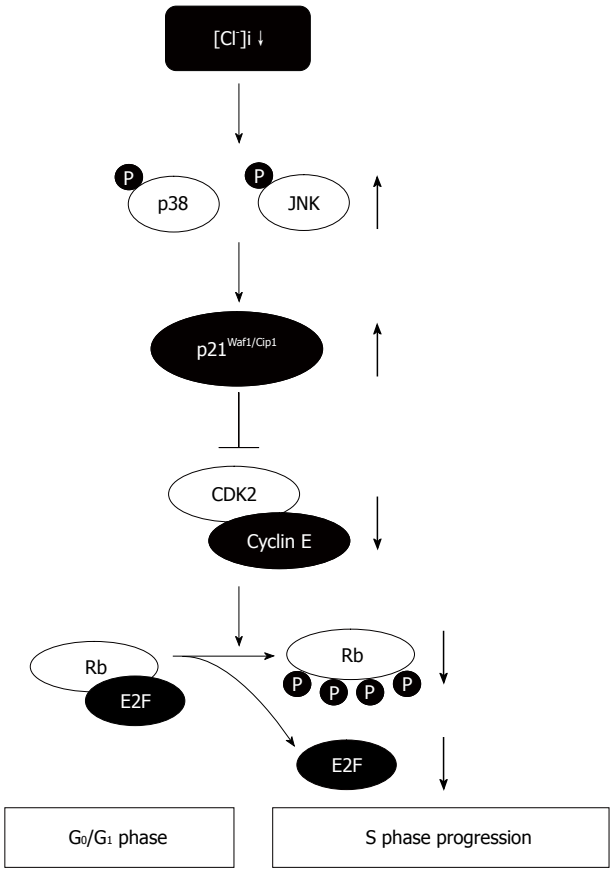


Figure 3 Roles of the intracellular chloride concentration in cell cycle progression of gastric cancer cells. The intracellular chloride concentration ($[Cl^-]_i$) affects the cell proliferation *via* activation of p38 and/or JNK cascades through upregulation of the p21. The decrease of the $[Cl^-]_i$ causes the G_0/G_1 phase arrest by diminishing expression of CDK2 and phosphorylated Rb due to an increase in expression of p21.

$[Cl^-]_i$ REGULATES p21 THROUGH THE ACTIVATION OF MAPKs IN GASTRIC CANCER CELLS

Generally, the induction of p21 is known to be dependent on tumor suppressor protein, p53, leading us to an idea that the upregulation of p21 induced by the decrease of the $[Cl^-]_i$ is due to activation of p53. However, the total expression and phosphorylation of p53 protein were not affected by application of the low Cl^- medium[18], indicating that the upregulation of p21 induced by the decrease of the $[Cl^-]_i$ was not dependent on activation of p53.

Therefore, we determined that MAPKs are involved in the p21 upregulation and cell cycle arrest induced by reduction of the $[Cl^-]_i$. Culture of MKN28 cells in the low Cl^- medium significantly induced phosphorylation

of MAPKs (ERK, p38, and JNK)[20]. Treatment with an inhibitor of p38 or JNK significantly suppressed p21 upregulation caused by culture in the low Cl^- medium and rescued MKN28 cells from the low Cl^--induced G_1 cell cycle arrest, whereas treatment with an ERK inhibitor had no significant effect on p21 expression or the growth of MKN28 cells in the low Cl^- medium[20]. These results suggest that the $[Cl^-]_i$ affects the cell proliferation *via* activation of p38 and/or JNK cascades through upregulation of the p21 in gastric cancer cells (Figure 3).

CONCLUSION

We showed that: (1) chloride has significant effects on cell cycle progress in human gastric cancer cells; (2) the decrease of the $[Cl^-]_i$ causes the G_0/G_1 phase arrest by diminishing expression of CDK2 and phosphorylated Rb due to an increase in expression of p21; (3) the $[Cl^-]_i$ has significant effects on the activity of MAPKs cascades; and (4) the activation of p38 and JNK by a low Cl^- condition leads to growth inhibition *via* an increase of p21 expression. Our results suggest that the $[Cl^-]_i$ regulates intracellular signaling cascades participating in the control of proliferation in gastric cancer cells. A deeper understanding of these mechanisms may lead to the discovery of the $[Cl^-]_i$ as an important mediator in tumor development and as a novel therapeutic target for gastric cancer.

REFERENCES

1 **Russell JM**. Sodium-potassium-chloride cotransport. *Physiol Rev* 2000; **80**: 211-276
2 **Kunzelmann K**. Ion channels and cancer. *J Membr Biol* 2005; **205**: 159-173
3 **Schönherr R**. Clinical relevance of ion channels for diagnosis and therapy of cancer. *J Membr Biol* 2005; **205**: 175-184
4 **Abdul M**, Hoosein N. Voltage-gated potassium ion channels in colon cancer. *Oncol Rep* 2002; **9**: 961-964
5 **Lastraioli E**, Guasti L, Crociani O, Polvani S, Hofmann G, Witchel H, Bencini L, Calistri M, Messerini L, Scatizzi M, Moretti R, Wanke E, Olivotto M, Mugnai G, Arcangeli A. herg1 gene and HERG1 protein are overexpressed in colorectal cancers and regulate cell invasion of tumor cells. *Cancer Res* 2004; **64**: 606-611
6 **Kim CJ**, Cho YG, Jeong SW, Kim YS, Kim SY, Nam SW, Lee SH, Yoo NJ, Lee JY, Park WS. Altered expression of KCNK9 in colorectal cancers. *APMIS* 2004; **112**: 588-594
7 **Shao XD**, Wu KC, Hao ZM, Hong L, Zhang J, Fan DM. The potent inhibitory effects of cisapride, a specific blocker for human ether-a-go-go-related gene (HERG) channel, on gastric cancer cells. *Cancer Biol Ther* 2005; **4**: 295-301
8 **Wang XT**, Nagaba Y, Cross HS, Wrba F, Zhang L, Guggino SE. The mRNA of L-type calcium channel elevated in colon cancer: protein distribution in normal and cancerous colon. *Am J Pathol* 2000; **157**: 1549-1562
9 **Tsavaler L**, Shapero MH, Morkowski S, Laus R. Trp-p8, a novel prostate-specific gene, is up-regulated in prostate cancer and other malignancies and shares high homology with transient receptor potential calcium channel proteins. *Cancer Res* 2001; **61**: 3760-3769
10 **Bustin SA**, Li SR, Dorudi S. Expression of the Ca2+-activated chloride channel genes CLCA1 and CLCA2 is downregulated in human colorectal cancer. *DNA Cell Biol* 2001; **20**: 331-338
11 **Sarosi GA**, Jaiswal K, Herndon E, Lopez-Guzman C, Spechler SJ, Souza RF. Acid increases MAPK-mediated proliferation in Barrett's esophageal adenocarcinoma cells via intracellular acidification through a Cl-/HCO3- exchanger. *Am J Physiol Gastrointest Liver Physiol* 2005; **289**: G991-G997
12 **Shiozaki A**, Miyazaki H, Niisato N, Nakahari T, Iwasaki Y, Itoi H, Ueda Y, Yamagishi H, Marunaka Y. Furosemide, a blocker of Na+/K+/2Cl- cotransporter, diminishes proliferation of poorly differentiated human gastric cancer cells by affecting G0/G1 state. *J Physiol Sci* 2006; **56**: 401-406
13 **Niisato N**, Eaton DC, Marunaka Y. Involvement of cytosolic Cl- in osmoregulation of alpha-ENaC gene expression. *Am J Physiol Renal Physiol* 2004; **287**: F932-F939
14 **Heimlich G**, Cidlowski JA. Selective role of intracellular chloride in the regulation of the intrinsic but not extrinsic pathway of apoptosis in Jurkat T-cells. *J Biol Chem* 2006; **281**: 2232-2241
15 **Yang T**, Park JM, Arend L, Huang Y, Topaloglu R, Pasumarthy A, Praetorius H, Spring K, Briggs JP, Schnermann J. Low chloride stimulation of prostaglandin E2 release and cyclooxygenase-2 expression in a mouse macula densa cell line. *J Biol Chem* 2000; **275**: 37922-37929
16 **Hiraoka K**, Miyazaki H, Niisato N, Iwasaki Y, Kawauchi A, Miki T, Marunaka Y. Chloride ion modulates cell proliferation of human androgen-independent prostatic cancer cell. *Cell Physiol Biochem* 2010; **25**: 379-388
17 **Miyazaki H**, Shiozaki A, Niisato N, Marunaka Y. Physiological significance of hypotonicity-induced regulatory volume decrease: reduction in intracellular Cl- concentration acting as an intracellular signaling. *Am J Physiol Renal Physiol* 2007; **292**: F1411-F1417
18 **Miyazaki H**, Shiozaki A, Niisato N, Ohsawa R, Itoi H, Ueda Y, Otsuji E, Yamagishi H, Iwasaki Y, Nakano T, Nakahari T, Marunaka Y. Chloride ions control the G1/S cell-cycle checkpoint by regulating the expression of p21 through a p53-independent pathway in human gastric cancer cells. *Biochem Biophys Res Commun* 2008; **366**: 506-512
19 **Maki M**, Miyazaki H, Nakajima K, Yamane J, Niisato N, Morihara T, Kubo T, Marunaka Y. Chloride-dependent acceleration of cell cycle via modulation of Rb and cdc2 in osteoblastic cells. *Biochem Biophys Res Commun* 2007; **361**: 1038-1043
20 **Ohsawa R**, Miyazaki H, Niisato N, Shiozaki A, Iwasaki Y, Otsuji E, Marunaka Y. Intracellular chloride regulates cell proliferation through the activation of stress-activated protein kinases in MKN28 human gastric cancer cells. *J Cell Physiol* 2010; **223**: 764-770

S- Editor Wang JL **L- Editor** Roemmele A **E- Editor** Zheng XM

World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v3.i8.123

World J Gastrointest Oncol 2011 August 15; 3(8): 123-127
ISSN 1948-5204 (online)

REVIEW

Emerging role of vitamin D in colorectal cancer

Wonmo Kang, Sujin Lee, Eunyi Jeon, Ye-Rang Yun, Kook-Hyun Kim, Jun-Hyeog Jang

Wonmo Kang, Sujin Lee, Eunyi Jeon, Ye-Rang Yun, Jun-Hyeog Jang, Department of Biochemistry, School of Medicine, Inha University, Incheon 400-712, South Korea
Kook-Hyun Kim, Department of Internal Medicine, College of Medicine, CHA University, Gumi 730-040, South Korea
Author contributions: Kang W, Lee S, Jeon E, Yun YR and Kim KH equally contributed to this paper; Jang JH wrote the paper.
Supported by Inha University Research Grant
Correspondence to: Jun-Hyeog Jang, PhD, Department of Biochemistry, School of Medicine, Inha University, Incheon 400-712, South Korea. juhjang@inha.ac.kr
Telephone: +82-32-8900933 Fax: +82-32-8821877
Received: April 15, 2011 Revised: July 25, 2011
Accepted: August 1, 2011
Published online: August 15, 2011

Abstract

Colorectal cancer is a common cancer and the fourth leading cause of death in Korea. The incidence and mortality of colorectal cancer varies according to risk factors, such as age, family history, genetic history, food habits, and physical activities. Some studies have focused on the association between vitamin D and colorectal cancer. Today, there is growing evidence that high vitamin D intake and a plasma level of 25(OH)D_3 reduce the incidence of colorectal cancer by modifying cancer angiogenesis, cell apoptosis, differentiation, and proliferation. Taken together, these results suggest that vitamin D supplementation alone, or in combination with anti-cancer agents, might reduce the incidence of colorectal cancer. In this review, we discuss the function and mechanism of vitamin D including the effect of vitamin D on colorectal cancer.

Key words: Colorectal cancer; Vitamin D; Vitamin D receptor; 25-hydroxyvitamin D; 1,25(OH)$_2$D$_3$

Peer reviewers: Runjan Chetty, Professor, Department of Pathology and Gene Regulation, University of Glasgow, Western Infirmary (Pathology), Dumbarton Road, Glasgow, G11 6NT, Scotland, United Kingdom; Ioannis A Voutsadakis, MD, PhD, Department of Medical Oncology, University Hospital of Larissa, Larissa 41110, Greece

Kang W, Lee S, Jeon E, Yun YR, Kim KH, Jang JH. Emerging role of vitamin D in colorectal cancer. *World J Gastrointest Oncol* 2011; 3(8): 123-127 Available from: URL: http://www.wjgnet.com/1948-5204/full/v3/i8/123.htm DOI: http://dx.doi.org/10.4251/wjgo.v3.i8.123

INTRODUCTION

Cancer of the colon or rectum is called colorectal cancer. It is a common cancer and the fourth leading cause of cancer-related death in the world. Colorectal cancer is also the third most common cancer in men and the second in women worldwide. It counted for an estimated, 1.2 million new cases and 0.6 million deaths in 2008[1]. In addition, colorectal cancer is the second leading cause of cancer death in the United States. Colorectal cancer incidence rates are rapidly increasing in several historically low risk areas including Spain, and a number of countries within Eastern Asia and Eastern Europe[2]. The risk factors for colorectal cancer are age, family history, and lifestyle, such as food habits and physical activities.

Vitamin D is associated with bone growth. Vitamin D insufficiency causes abnormal bone growth, while sufficiency prevents rickets and osteomalacia, as well as osteoporosis. Vitamin D enhances the immune system[3]. In addition, vitamin D is known to prevent cancer[4] and cardiovascular diseases[5]. Vitamin D and its analogues have the ability to prevent cancer *in vitro* and in animal models. However, the anti-cancer effect of dietary vitamin D remains controversial. Recently, a study reported that vitamin D is not effective in preventing cancer and cardiovascular diseases[6]. Of vitamin D forms, 1,25(OH)$_2$D$_3$ (calciferol) induces biological effects by binding to the vitamin D receptor (VDR). The activation of VDR leads

to the maintenance of calcium and phosphorus levels in the blood as well as of bone content. VDR is also involved in cell proliferation and differentiation.

For more than 20 years, epidemiological, experimental and clinical studies have shown that vitamin D has significant protective effect against the development of cancer[4]. The mechanism of vitamin D works through several molecular pathways, such as growth-factor signaling, and transforming growth factor-β-SMAD signaling. The anti-cancer activities of vitamin D exerted by $1,25(OH)_2D_3$ are produced by regulating the cell cycle, apoptosis, and adhesion, as well as by cellular differentiation and proliferation. Interestingly, vitamin D reduces the incidence of colorectal cancer, when vitamin D intake, the plasma level of $25(OH)D_3$ and UV exposure is particularly high. In addition, the combination of vitamin D with other anti-cancer agents efficiently controls the development of colorectal cancer growth[7].

Here, the function and mechanism of vitamin D is briefly introduced, and the beneficial effect of vitamin D on colorectal cancer is discussed.

CLASSIFICATION AND MOLECULAR GENETICS OF COLORECTAL CANCER

The molecular pathogenesis of colorectal cancer has been one of the most prominent study areas in recent years. Colorectal cancer exhibits two major forms: sporadic colorectal cancer and inherited colorectal cancer.

First, sporadic cancer occurs in people who have no family history or very little of the disease. Although cancer sometimes has a hereditary or familial component, it is not common. Approximately 70%-75% of colorectal cancer is sporadic cancer. Second, inherited colorectal cancer comprises familial and hereditary cancer. Familial and hereditary cancer cancer occurs in families who have a faulty gene inherited from the father or mother. Generally, 5% of colorectal cancer is familial cancer. Familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer are the two forms of inherited colorectal cancer[8].

Ten to thirty percent of cases are attributed to familial risk and the rest to sporadic cancer. The majority of cancers are considered to be sporadic cancer. As stated above, most colorectal cancers are sporadic cancer, and only 5%-10% are inherited cancers.

FUNCTIONS OF VITAMIN D

Vitamin D exerts its various functions through molecular pathways. Vitamin D pathways are highly complex. The factors, affecting the vitamin D pathway, are P21, P27, CDKs, P53, BRCA-1.-2, ß-catenin and c-myc. Depending on which factor, vitamin D is involved in cell adhesion, apoptosis, differentiation and division[9]. Primarily, vitamin D plays an important role in muscle and bone health. Vitamin D deficiency results in impaired bone mineralization and leads to bone softening diseases including rickets and osteomalacia[10]. Further, vitamin D deficiency is involved in high bone turnover[11]. Vitamin D deficiency can also play a role in the pathogenesis of auto-immune diseases such as multiple sclerosis, diabetes type 1, cancer[12] and cardiovascular disease[13]. Conversely, vitamin D deficiency increases parathyroid hormone levels leading to mobilization of calcium from bone, thereby compromising bone development in the adolescent[14]. In contrast, vitamin D supplementation enhances bone density[15]. Next, vitamin D exerts an anti-cancer activity[16]. These activities of vitamin D functions are regulated by circulating vitamin D forms, the increasing concentration of $25(OH)D_3$ and increasing activity of $1,25(OH)_2D_3$. Vitamin D induces cellular proliferation, differentiation, and apoptosis of cancer and normal cells through the regulatory mechanism[17-19]. These studies show that low intake levels of vitamin D increase the risk of colorectal cancer. Some studies show vitamin D exerts growth-restraining, anti-carcinogenic effects on colorectal cancer[20,21]. In addition, vitamin D affects growth factors, regulation of cell division, cytokine synthesis, signaling, cell cycle control, and apoptosis pathway[5,22]. In a study *in vitro*, a similar result was reported. When LOVO cells were treated for 8 d with various concentrations of $1,25(OH)_2D_3$, cell proliferation was inhibited significantly[23].

Table 1 summarizes the anti-cancer effects of vitamin D *in vivo* in mice and rats.

MECHANISM OF VITAMIN D IN COLORECTAL CANCER

Vitamin D and its metabolites reduce the incidence of various cancers by inhibiting cancer angiogenesis, stimulating normal cells[33-37] and also by promoting the inhibition of proliferation. Vitamin D metabolites also help to maintain a standard calcium gradient in the various colonic epithelial cells. High levels of blood serum $25(OH)D_3$ are associated with a noticeable decrease in proliferation of non-cancerous cells[38,39]. The anti-proliferative effect of vitamin D is attained by inducing G1 cell-cycle arrest, which is probably mediated by up-regulation of cell cycle inhibitors. Vitamin D modulates the activation of these cell cycle related genes by various mechanisms. Vitamin D also exerts anti-carcinogenic effects by interfering with the synthesis of growth factors and cytokines and by modulating their signaling pathways. In addition to the growth inhibitory effects, vitamin D induces the differentiation of colon cancer cells. The $1,25(OH)_2D_3$ and its analogs exert anti-carcinogenic activities in human colon cancer cells by inhibition of proliferation and induction of differentiation and apoptosis[22]. The $1,25(OH)_2D_3$ significantly increases the expression and activity of alkaline phosphatase, a marker of colonic differentiation. VDR activation by $1,25(OH)_2D_3$ produces changes in stick junction integrity, increases differentiation and reduces oncogenic cell signaling. Induction of these genes affects cell oncogenesis, and tissue development. Thus, treatment with $1,25(OH)_2D_3$ supresses oncogenic genes in

Table 1 Anti-cancer effects of vitamin D in various rodent models

Treatment	Inducer	Species	Results	Ref.
Supplement		VDR knockout mouse	Inhibition of hyperproliferation and adenoma formation	[24]
Supplement		Apc1638 mice	Inhibition of carcinoma incidence	[25]
Deficiency		Balb/C mice	Enhancement of cancer cell growth	[26]
Supplement		Balb/C mice	Inhibition of tumor growth	[27]
Supplement		C57BL/6J mice	Inhibition of hyperproliferation Inhibition of tumor incidence	[28]
Deficiency	DMH	SD rat	No effect	[29]
Deficiency		SD rat	Enhancement of carcinogenesis	[30]
Supplement	DMH	Fisher344 rat	No effect	[31]
Supplement	DMH	Fisher344 rat	Inhibition of tumor incidence	[32]

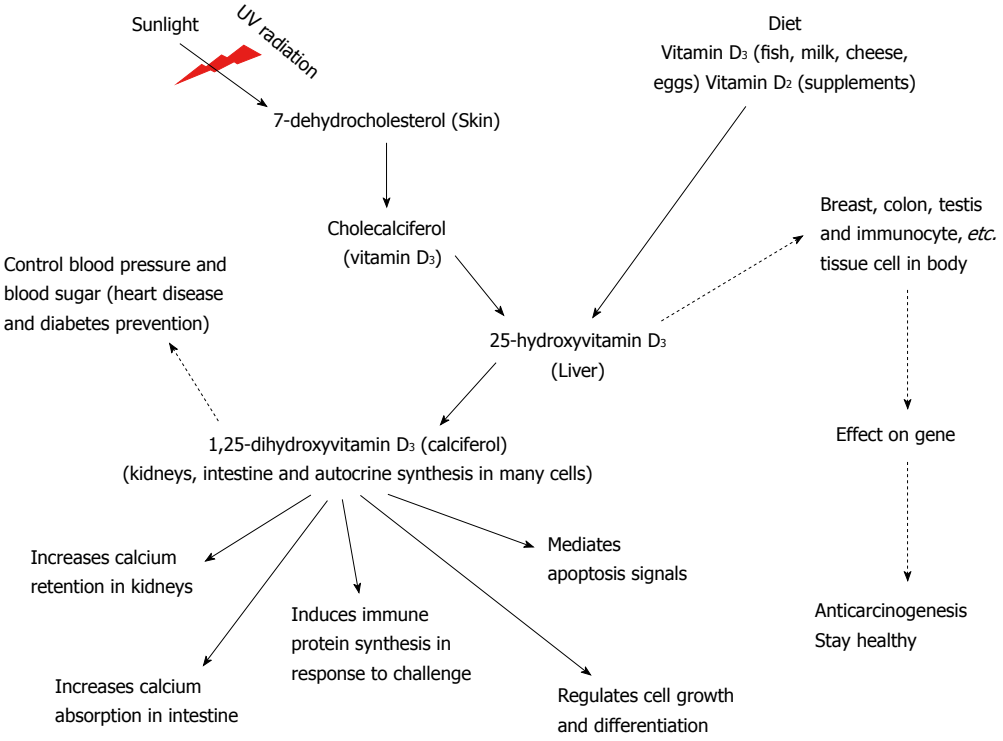


Figure 1 Mechanisms of vitamin D in various tissues.

colon cancer cells. Finally, VDR genotypes are associated with anti-cancer activity in colorectal cancer. There are several VDR genotypes. For example, the most important VDR genotype is Bsm I, which has 3 variants: BB, Bb, and bb in America. The bb genotype is associated with lower concentrations of circulating $1,25(OH)_2D_3$, leading to an increased incidence of colorectal cancer[40,41]. Taken together, these observations demonstrate that vitamin D exerts anti-cancer activity in colon cancer.

Figure 1 describes the mechanisms of vitamin D in various tissues. In the figure, the dotted arrow shows a newly discovered function of vitamin D.

SUMMARY AND CONCLUSIONS

Previous research has shown the efficacy of taking vitamin D for reducing cancer risk[42]. There is strong evidence that vitamin D can change and inhibit the development of colon cancers[22]. These protective effects are likely due to the regulatory effects of 1,25-dihydroxyvitamin D_3 (calciferol) on cellular mechanisms involved in cancer development, including apoptosis, cell adhesion, cell cycle control, regulation of cellular differentiation and proliferation. A clinical study group will set up guidelines for vitamin D intake and develop models to define levels of serum $25(OH)D_3$ that prevent the growth of cancer. Elevation of vitamin D levels may protect against diverse cancers. Many studies show that vitamin D assists in prevention and therapy of cancer[9]. The new guidelines will lead to more effective physical condition policies, resulting in substantially fewer cases of cancer of the colon in the future[5].

REFERENCES

1 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer sta-

tistics, 2009. *CA Cancer J Clin* 2009; **59**: 225-249
2 **Center MM**, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *CA Cancer J Clin* 2009; **59**: 366-378
3 **Munger KL**, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA* 2006; **296**: 2832-2838
4 **Ingraham BA**, Bragdon B, Nohe A. Molecular basis of the potential of vitamin D to prevent cancer. *Curr Med Res Opin* 2008; **24**: 139-149
5 **Melamed ML**, Muntner P, Michos ED, Uribarri J, Weber C, Sharma J, Raggi P. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. *Arterioscler Thromb Vasc Biol* 2008; **28**: 1179-1185
6 **Manson JE**, Mayne ST, Clinton SK. Vitamin D and prevention of cancer--ready for prime time? *N Engl J Med* 2011; **364**: 1385-1387
7 **Cross HS**, Nittke T, Peterlik M. Modulation of vitamin D synthesis and catabolism in colorectal mucosa: a new target for cancer prevention. *Anticancer Res* 2009; **29**: 3705-3712
8 **Lynch HT**, de la Chapelle A. Hereditary colorectal cancer. *N Engl J Med* 2003; **348**: 919-932
9 **Bulathsinghala P**, Syrigos KN, Saif MW. Role of vitamin d in the prevention of pancreatic cancer. *J Nutr Metab* 2010; **2010**: 721365
10 **Ebeling PR**. Megadose therapy for vitamin D deficiency. *Med J Aust* 2005; **183**: 4-5
11 **Diamond TH**, Levy S, Smith A, Day P. High bone turnover in Muslim women with vitamin D deficiency. *Med J Aust* 2002; **177**: 139-141
12 **Lips P**. Vitamin D physiology. *Prog Biophys Mol Biol* 2006; **92**: 4-8
13 **Zittermann A**. Vitamin D and disease prevention with special reference to cardiovascular disease. *Prog Biophys Mol Biol* 2006; **92**: 39-48
14 **Harkness L**, Cromer B. Low levels of 25-hydroxy vitamin D are associated with elevated parathyroid hormone in healthy adolescent females. *Osteoporos Int* 2005; **16**: 109-113
15 **Working Group of the Australian and New Zealand Bone and Mineral Society**; Endocrine Society of Australia; Osteoporosis Australia. Vitamin D and adult bone health in Australia and New Zealand: a position statement. *Med J Aust* 2005; **182**: 281-285
16 **Trivedi DP**, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003; **326**: 469
17 **Lamprecht SA**, Lipkin M. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. *Ann N Y Acad Sci* 2001; **952**: 73-87
18 **Studzinski GP**, McLane JA, Uskoković MR. Signaling pathways for vitamin D-induced differentiation: implications for therapy of proliferative and neoplastic diseases. *Crit Rev Eukaryot Gene Expr* 1993; **3**: 279-312
19 **Ylikomi T**, Laaksi I, Lou YR, Martikainen P, Miettinen S, Pennanen P, Purmonen S, Syvälä H, Vienonen A, Tuohimaa P. Antiproliferative action of vitamin D. *Vitam Horm* 2002; **64**: 357-406
20 **Bostick RM**, Potter JD, Sellers TA, McKenzie DR, Kushi LH, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to incidence of colon cancer among older women. The Iowa Women's Health Study. *Am J Epidemiol* 1993; **137**: 1302-1317
21 **Zheng W**, Anderson KE, Kushi LH, Sellers TA, Greenstein J, Hong CP, Cerhan JR, Bostick RM, Folsom AR. A prospective cohort study of intake of calcium, vitamin D, and other micronutrients in relation to incidence of rectal cancer among postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 1998; **7**: 221-225
22 **Lamprecht SA**, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat Rev Cancer* 2003; **3**: 601-614
23 **Lointier P**, Wargovich MJ, Saez S, Levin B, Wildrick DM, Boman BM. The role of vitamin D3 in the proliferation of a human colon cancer cell line in vitro. *Anticancer Res* 1987; **7**: 817-821
24 **Kallay E**, Pietschmann P, Toyokuni S, Bajna E, Hahn P, Mazzucco K, Bieglmayer C, Kato S, Cross HS. Characterization of a vitamin D receptor knockout mouse as a model of colorectal hyperproliferation and DNA damage. *Carcinogenesis* 2001; **22**: 1429-1435
25 **Lipkin M**, Yang K, Edelmann W, Newmark H, Fan KH, Risio M, Kucherlapati R. Inherited and acquired risk factors in colonic neoplasia and modulation by chemopreventive interventions. *J Cell Biochem Suppl* 1996; **25**: 136-141
26 **Tangpricha V**, Spina C, Yao M, Chen TC, Wolfe MM, Holick MF. Vitamin D deficiency enhances the growth of MC-26 colon cancer xenografts in Balb/c mice. *J Nutr* 2005; **135**: 2350-2354
27 **Spina C**, Tangpricha V, Yao M, Zhou W, Wolfe MM, Maehr H, Uskokovic M, Adorini L, Holick MF. Colon cancer and solar ultraviolet B radiation and prevention and treatment of colon cancer in mice with vitamin D and its Gemini analogs. *J Steroid Biochem Mol Biol* 2005; **97**: 111-120
28 **Newmark HL**, Yang K, Kurihara N, Fan K, Augenlicht LH, Lipkin M. Western-style diet-induced colonic tumors and their modulation by calcium and vitamin D in C57Bl/6 mice: a preclinical model for human sporadic colon cancer. *Carcinogenesis* 2009; **30**: 88-92
29 **Sitrin MD**, Halline AG, Abrahams C, Brasitus TA. Dietary calcium and vitamin D modulate 1,2-dimethylhydrazine-induced colonic carcinogenesis in the rat. *Cancer Res* 1991; **51**: 5608-5613
30 **Millan MJ**, Bervoets K, Colpaert FC. 5-hydroxytryptamine (5-HT)1A receptors and the tail-flick response. I. 8-hydroxy-2-(di-n-propylamino) tetralin HBr-induced spontaneous tail-flicks in the rat as an in vivo model of 5-HT1A receptor-mediated activity. *J Pharmacol Exp Ther* 1991; **256**: 973-982
31 **Comer PF**, Clark TD, Glauert HP. Effect of dietary vitamin D3 (cholecalciferol) on colon carcinogenesis induced by 1,2-dimethylhydrazine in male Fischer 344 rats. *Nutr Cancer* 1993; **19**: 113-124
32 **Beaty MM**, Lee EY, Glauert HP. Influence of dietary calcium and vitamin D on colon epithelial cell proliferation and 1,2-dimethylhydrazine-induced colon carcinogenesis in rats fed high fat diets. *J Nutr* 1993; **123**: 144-152
33 **Iseki K**, Tatsuta M, Uehara H, Iishi H, Yano H, Sakai N, Ishiguro S. Inhibition of angiogenesis as a mechanism for inhibition by 1alpha-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 of colon carcinogenesis induced by azoxymethane in Wistar rats. *Int J Cancer* 1999; **81**: 730-733
34 **Majewski S**, Skopinska M, Marczak M, Szmurlo A, Bollag W, Jablonska S. Vitamin D3 is a potent inhibitor of tumor cell-induced angiogenesis. *J Investig Dermatol Symp Proc* 1996; **1**: 97-101
35 **Shokravi MT**, Marcus DM, Alroy J, Egan K, Saornil MA, Albert DM. Vitamin D inhibits angiogenesis in transgenic murine retinoblastoma. *Invest Ophthalmol Vis Sci* 1995; **36**: 83-87
36 **Mantell DJ**, Owens PE, Bundred NJ, Mawer EB, Canfield AE. 1 alpha,25-dihydroxyvitamin D(3) inhibits angiogenesis in vitro and in vivo. *Circ Res* 2000; **87**: 214-220
37 **Pálmer HG**, González-Sancho JM, Espada J, Berciano MT, Puig I, Baulida J, Quintanilla M, Cano A, de Herreros AG, Lafarga M, Muñoz A. Vitamin D(3) promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of beta-catenin signaling. *J Cell Biol* 2001; **154**: 369-387
38 **Lipkin M**, Newmark H. Effect of added dietary calcium on

colonic epithelial-cell proliferation in subjects at high risk for familial colonic cancer. *N Engl J Med* 1985; **313**: 1381-1384

39 **Holt PR**, Arber N, Halmos B, Forde K, Kissileff H, McGlynn KA, Moss SF, Kurihara N, Fan K, Yang K, Lipkin M. Colonic epithelial cell proliferation decreases with increasing levels of serum 25-hydroxy vitamin D. *Cancer Epidemiol Biomarkers Prev* 2002; **11**: 113-119

40 **Ma J**, Stampfer MJ, Gann PH, Hough HL, Giovannucci E, Kelsey KT, Hennekens CH, Hunter DJ. Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians. *Cancer Epidemiol Biomarkers Prev* 1998; **7**: 385-390

41 **Slatter ML**, Yakumo K, Hoffman M, Neuhausen S. Variants of the VDR gene and risk of colon cancer (United States). *Cancer Causes Control* 2001; **12**: 359-364

42 **Lilliu H**, Pamphile R, Chapuy MC, Schulten J, Arlot M, Meunier PJ. Calcium-vitamin D3 supplementation is cost-effective in hip fractures prevention. *Maturitas* 2003; **44**: 299-305

S- Editor Wang JL **L- Editor** Hughes D **E- Editor** Zheng XM

World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
www.wjgnet.com

World J Gastrointest Oncol 2011 August 15; 3(8): I
ISSN 1948-5204 (online)

Acknowledgments to reviewers of *World Journal of Gastrointestinal Oncology*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Gastrointestinal Oncology*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

Antonio Russo, MD, PhD, Associate Professor, Genetic and Molecular Oncology Unit, Interdepartmental Center of Research in Clinical Oncology, School of Medicine, University of Palermo, Via del Vespro 127-90127 Palermo, Italy

Masayuki Ohtsuka, MD, PhD, Department of General Surgery, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuoh-ku, Chiba 260-8670, Japan

Goran Stanojevic, MD, PhD, Professor, Department of Surgery, Clinical Centre Nis, Bul Zorana Djindjica 48, 18000 Nis, Serbia

Jian-Kun Hu, MD, PhD, Associate Professor, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Atsushi Imagawa, MD, Department of Gastroenterology, Tsuyama Central Hospital, 1756 Kawasaki Tsuyama-city, Okayama 708-0841, Japan

Runjan Chetty, Professor, Department of Pathology and Gene Regulation, University of Glasgow, Western Infirmary (Pathology), Dumbarton Road, Glasgow, G11 6NT, Scotland, United Kingdom

John Griniatsos, MD, Assistant Professor, Department of Surgery, University of Athens, Medical School, 1st LAIKO Hospital, 17 Agiou Thoma str, GR 115-27, Athens, Greece

Kwang-Huei Lin, PhD, Professor, Associate Dean, College of Medicine, Chang-Gung University, 259 Wen-Hwa 1st Road, Taoyuan 333, Taiwan, China

Barbara W Chwirot, Professor, Department of Medical Biology, Institute of General and Molecular Biology, Nicolaus Copernicus University, Gagarina 9, Torun 87-100, Poland

Ioannis D Kanellos, Professor, 4th Surgical Department, Aristotle University of Thessaloniki, Antheon 1, Thessaloniki 55236, Greece

Fahd Al-Mulla, PhD, Associate Professor, Department of Molecular Pathology, Kuwait University, Faculty of Medicine, Safat 13110, Kuwait

Ioannis A Voutsadakis, MD, PhD, Department of Medical Oncology, University Hospital of Larissa, Larissa 41110, Greece

Seung Joon Baek, PhD, Associate Professor, Department of Pathobiology, College of Veterinary Medicine, The University of Tennessee, 2407 River Drive, Rm A228, Knoxville, TN 37996, United States

WJGO

World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
www.wjgnet.com

World J Gastrointest Oncol 2011 August 15; 3(8): I
ISSN 1948-5204 (online)

Events Calendar 2011

January 20-22, 2011
Gastrointestinal Cancers Symposium 2011, San Francisco, CA, United States

January 27-28, 2011
Falk Workshop, Liver and Immunology, Medical University, Regensburg, Germany

February 17-20, 2011
APASL 2011-The 21st Conference of the Asian Pacific Association for the Study of the Liver, Bangkok, Thailand

February 21-21, 2011
International Conference on Modern Cancer Management-Joint Symposium, Abuja, Nigeria,

February 26-March 1, 2011
Canadian Digestive Diseases Week, Westin Bayshore, Vancouver, British Columbia, Canada

March 11-12, 2011
First Integrative Care for the Future: The future of cancer care, Arnhem, The Netherlands
http://www.integrativecareftfuture.org/

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011, Birmingham, England, United Kingdom

March 24-25, 2011
Advanced Cancer Course "International Clinical Trials Workshop", Punta del Este, Uruguay

April 6-7, 2011
IBS-A Global Perspective, Milwaukee, WI, United States

April 6-8, 2011
Third Latin American Symposium on Gastrointestinal Oncology-Chilean Foundation for Oncology Development Joint Symposium, Vina Del Mar, Chile

April 15-16, 2011
Falk Symposium 177, Endoscopy Live Berlin 2011 Intestinal Disease Meeting, Maritim Hotel Berlin, Stauffenbergstr. 26, 10785 Berlin, Germany

April 20-23, 2011
9th International Gastric Cancer Congress, COEX, World Trade Center, Samseong-dong, Gangnam-gu, Seoul 135-731, South Korea

May 8-12, 2011
ESTRO International Oncology Forum, London, United Kingdom

May 19-22, 2011
1st World Congress on Controversies in the Management of Viral Hepatitis (C-Hep), Palau de Congressos de Catalunya, Barcelona, Spain

May 25–27, 2011
9th CIMT Annual Meeting, Targeting Cancer, Road-Maps for Success, Mainz, Germany

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Sarajevo, Bosnia and Herzegovina

June 3-7, 2011
2011 ASCO Annual Meeting, Chicago, IL, United States

June 18-24, 2011
13th Joint ECCO-AACR-EORTC-ESMO Workshop on "Methods in Clinical Cancer Research", Flims, Switzerland

June 22-25, 2011
ESMO 13th World Congress on Gastrointestinal Cancer, Barcelona, Spain

July 9-10, 2011
Best of ASCO China, Hengzhou, China

July 21-23, 2011
ASCO-JSMO Joint Symposium, Yokohama, Japan

August 25-28, 2011
VII Peruvian Congress SPOM: Toward personalized Oncology-Endorsement, Lima, Peru

September 2-3, 2011
Falk Symposium 178, Diverticular Disease, A Fresh Approach to a Neglected Disease, Martinstr. 29-37, 50667 Cologne, Germany

September 10-14, 2011
ICE 2011-International Congress of Endoscopy, Los Angeles Convention Center, 1201 South Figueroa Street, Los Angeles, CA, United States

September 15-17, 2011
2011 Gastrointestinal Oncology Conference, Sheraton Crystal City, Arlington, VA, United States

September 30-October 1, 2011
Falk Symposium 179, Revisiting IBD Management: Dogmas to be Challenged, Place Rogier 3, 1210 Brussels, Belgium, Germany

October 6-7, 2011
IV InterAmerican Oncology Conference: Current Status and Future of Anti-Cancer Targeted Therapies, Buenos Aires, Argentina

October 14-15, 2011
New Trends in the Medical Treatment of Solid Malignancy-Romanian Society for Medical Oncology Joint Symposium, Bucharest, Romania

October 27-29, 2011
EORTC-NCI-ASCO Annual Meeting on Molecular Markers in Cancer, Brussels, Belgium

November 11-12, 2011
Falk Symposium 180, IBD 2011: Progress and Future for Lifelong Management, 1-12-33 Akasaka, Minato-ku, Tokyo 107-0052, Japan

November 30-December 3, 2011
8th International Cancer Conference "Entering the 21st Century for Cancer Control in Africa"-African Organization for Research and Training in Cancer Joint Symposium, Cairo, Egypt

WJGO World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
www.wjgnet.com

World J Gastrointest Oncol 2011 August 15; 3(8): I-V
ISSN 1948-5204 (online)

INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, ISSN 1948-5204, DOI: 10.4251), is a monthly, open-access (OA), peer-reviewed journal supported by an editorial board of 404 experts in gastrointestinal oncology from 41 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results. The open access model has been proven to be a true approach that may achieve the ultimate goal of the journals, i.e. the maximization of the value to the readers, authors and society.

Maximization of personal benefits

The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJGO* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article *via* online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJGO* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJGO* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

Aims and scope

The major task of *WJGO* is to report rapidly the most recent advances in basic and clinical research on gastrointestinal oncology. The topics of *WJGO* cover the carcinogenesis, tumorigenesis, metastasis, diagnosis, prevention, prognosis, clinical manifestations, nutritional support, molecular mechanisms, and therapy of benign and malignant tumors of the digestive tract. This cover epidemiology, etiology, immunology, molecular oncology, cytology, pathology, genetics, genomics, proteomics, pharmacology, pharmacokinetics, nutrition, diagnosis and therapeutics. This journal will also provide extensive and timely review articles on oncology.

Columns

The columns in the issues of *WJGO* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in gastrointestinal oncology; (9) Brief Articles: To briefly report the novel and innovative findings in cardiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJGO*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of gastrointestinal oncology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in gastrointestinal oncology.

Name of journal

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

Indexing/abstracting

PubMed Central, PubMed, Digital Object Identifer, and Directory of Open Access Journals.

Published by

Baishideng Publishing Group Co., Limited

SPECIAL STATEMENT

All articles published in this journal represent the viewpoints of the authors except where indicated otherwise.

Biostatistical editing

Statisital review is performed after peer review. We invite an expert in Biomedical Statistics from to evaluate the statistical method used in the paper, including *t*-test (group or paired comparisons), chi-squared test, Ridit, probit, logit, regression (linear, curvilinear, or stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

Conflict-of-interest statement

In the interests of transparency and to help reviewers assess any potential bias, *WJGO* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

Sample wording: [Name of individual] has received fees for serving as a speaker, a consultant and an advisory board member for [names of organizations], and has received research funding from [names of organization]. [Name of individual] is an employee of [name of organization]. [Name of individual] owns stocks and shares in [name of organization]. [Name of individual] owns patent [patent identification and brief description].

Statement of informed consent

Manuscripts should contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee or it should be stated clearly in the text that all persons gave their informed consent prior to their inclusion in the study. Details that might disclose the identity of the subjects under study should be omitted. Authors should also draw attention to the Code of Ethics of the World Medical Association (Declaration of Helsinki, 1964, as revised in 2004).

Statement of human and animal rights

When reporting the results from experiments, authors should follow the highest standards and the trial should comform to Good Clinical Practice (for example, US Food and Drug Administration Good Clinical Practice in FDA-Regulated Clinical Trials; UK Medicines Research Council Guidelines for Good Clinical Practice in Clinical Trials) and/or the World Medical Association Declaration of Helsinki. Generally, we suggest authors follow the lead investigator's national standard. If doubt exists whether the research was conducted in accordance with the above standards, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.

Before submitting, authors should make their study approved by the relevant research ethics committee or institutional review board. If human participants were involved, manuscripts must be accompanied by a statement that the experiments were undertaken with the understanding and appropriate informed consent of each. Any personal item or information will not be published without explicit consents from the involved patients. If experimental animals were used, the materials and methods (experimental procedures) section must clearly indicate that appropriate measures were taken to minimize pain or discomfort, and details of animal care should be provided.

SUBMISSION OF MANUSCRIPTS

Manuscripts should be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Number all pages consecutively, and start each of the following sections on a new page: Title Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables, Figures, and Figure Legends. Neither the editors nor the publisher are responsible for the opinions expressed by contributors. Manuscripts formally accepted for publication become the permanent property of Baishideng Publishing Group Co., Limited, and may not be reproduced by any means, in whole or in part, without the written permission of both the authors and the publisher. We reserve the right to copy-edit and put onto our website accepted manuscripts. Authors should follow the relevant guidelines for the care and use of laboratory animals of their institution or national animal welfare committee. For the sake of transparency in regard to the performance and reporting of clinical trials, we endorse the policy of the ICMJE to refuse to publish papers on clinical trial results if the trial was not recorded in a publicly-accessible registry at its outset. The only register now available, to our knowledge, is http://www.clinicaltrials.gov sponsored by the United States National Library of Medicine and we encourage all potential contributors to register with it. However, in the case that other registers become available you will be duly notified. A letter of recommendation from each author's organization should be provided with the contributed article to ensure the privacy and secrecy of research is protected.

Authors should retain one copy of the text, tables, photographs and illustrations because rejected manuscripts will not be returned to the author(s) and the editors will not be responsible for loss or damage to photographs and illustrations sustained during mailing.

Online submissions

Manuscripts should be submitted through the Online Submission System at: http://www.wjgnet.com/1948-5204office. Authors are highly recommended to consult the ONLINE INSTRUCTIONS TO AUTHORS (http://www.wjgnet.com/1948-5204/g_info_20100312180518.htm) before attempting to submit online. For assistance, authors encountering problems with the Online Submission System may send an email describing the problem to wjgo@wjgnet.com, or by telephone: +86-10-85381891. If you submit your manuscript online, do not make a postal contribution. Repeated online submission for the same manuscript is strictly prohibited.

MANUSCRIPT PREPARATION

All contributions should be written in English. All articles must be submitted using word-processing software. All submissions must be typed in 1.5 line spacing and 12 pt. Book Antiqua with ample margins. Style should conform to our house format. Required information for each of the manuscript sections is as follows:

Title page

Title: Title should be less than 12 words.

Running title: A short running title of less than 6 words should be provided.

Authorship: Authorship credit should be in accordance with the standard proposed by International Committee of Medical Journal Editors, based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

Institution: Author names should be given first, then the complete name of institution, city, province and postcode. For example, Xu-Chen Zhang, Li-Xin Mei, Department of Pathology, Chengde Medical College, Chengde 067000, Hebei Province, China. One author may be represented from two institutions, for example, George Sgourakis, Department of General, Visceral, and Transplantation Surgery, Es-

sen 45122, Germany; George Sgourakis, 2nd Surgical Department, Korgialenio-Benakio Red Cross Hospital, Athens 15451, Greece

Author contributions: The format of this section should be: Author contributions: Wang CL and Liang L contributed equally to this work; Wang CL, Liang L, Fu JF, Zou CC, Hong F and Wu XM designed the research; Wang CL, Zou CC, Hong F and Wu XM performed the research; Xue JZ and Lu JR contributed new reagents/analytic tools; Wang CL, Liang L and Fu JF analyzed the data; and Wang CL, Liang L and Fu JF wrote the paper.

Supportive foundations: The complete name and number of supportive foundations should be provided, e.g. Supported by National Natural Science Foundation of China, No. 30224801

Correspondence to: Only one corresponding address should be provided. Author names should be given first, then author title, affiliation, the complete name of institution, city, postcode, province, country, and email. All the letters in the email should be in lower case. A space interval should be inserted between country name and email address. For example, Montgomery Bissell, MD, Professor of Medicine, Chief, Liver Center, Gastroenterology Division, University of California, Box 0538, San Francisco, CA 94143, United States. montgomery.bissell@ucsf.edu

Telephone and fax: Telephone and fax should consist of +, country number, district number and telephone or fax number, e.g. Telephone: +86-10-85381891 Fax: +86-10-85381893

Peer reviewers: All articles received are subject to peer review. Normally, three experts are invited for each article. Decision for acceptance is made only when at least two experts recommend an article for publication. Reviewers for accepted manuscripts are acknowledged in each manuscript, and reviewers of articles which were not accepted will be acknowledged at the end of each issue. To ensure the quality of the articles published in *WJGO*, reviewers of accepted manuscripts will be announced by publishing the name, title/position and institution of the reviewer in the footnote accompanying the printed article. For example, reviewers: Professor Jing-Yuan Fang, Shanghai Institute of Digestive Disease, Shanghai, Affiliated Renji Hospital, Medical Faculty, Shanghai Jiaotong University, Shanghai, China; Professor Xin-Wei Han, Department of Radiology, The First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan Province, China; and Professor Anren Kuang, Department of Nuclear Medicine, Huaxi Hospital, Sichuan University, Chengdu, Sichuan Province, China.

Abstract

There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

An informative, structured abstracts of no more than 480 words should accompany each manuscript. Abstracts for original contributions should be structured into the following sections. AIM (no more than 20 words): Only the purpose should be included. Please write the aim as the form of "To investigate/study/…; MATERIALS AND METHODS (no more than 140 words); RESULTS (no more than 294 words): You should present *P* values where appropriate and must provide relevant data to illustrate how they were obtained, e.g. 6.92 ± 3.86 *vs* 3.61 ± 1.67, $P < 0.001$; CONCLUSION (no more than 26 words).

Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

For articles of these sections, original articles and brief articles, the main text should be structured into the following sections: INTRODUCTION, MATERIALS AND METHODS, RESULTS and DISCUSSION, and should include appropriate Figures and Tables. Data should be presented in the main text or in Figures and Tables, but not in both. The main text format of these sections, editorial, topic highlight, case report, letters to the editors, can be found at: http://www.wjgnet.com/1948-5204/g_info_list.htm.

Illustrations

Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

Tables

Three-line tables should be numbered 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each table. Detailed legends should not be included under tables, but rather added into the text where applicable. The information should complement, but not duplicate the text. Use one horizontal line under the title, a second under column heads, and a third below the Table, above any footnotes. Vertical and italic lines should be omitted.

Notes in tables and illustrations

Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

Coding system

The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

When the authors write the references, please ensure that the order in text is the same as in the references section, and also ensure the spelling accuracy of the first author's name. Do not list the same citation twice.

PMID and DOI

Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.

gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

Style for journal references

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

Style for book references

Authors: the name of the first author should be typed in bold-faced letters. The surname of all authors should be typed with the initial letter capitalized, followed by their abbreviated middle and first initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR) Book title. Publication number. Publication place: Publication press, Year: start page and end page.

Format

Journals

English journal article (list all authors and include the PMID where applicable)

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1948-5204/g_info_20100312183048.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length,

m mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

Examples for paper writing
Editorial: http://www.wjgnet.com/1948-5204/g_info_20100312180823.htm

Frontier: http://www.wjgnet.com/1948-5204/g_info_20100312181003.htm

Topic highlight: http://www.wjgnet.com/1948-5204/g_info_20100312181119.htm

Observation: http://www.wjgnet.com/1948-5204/g_info_20100312181227.htm

Guidelines for basic research: http://www.wjgnet.com/1948-5204/g_info_20100312181408.htm

Guidelines for clinical practice: http://www.wjgnet.com/1948-5204/g_info_20100312181552.htm

Review: http://www.wjgnet.com/1948-5204/g_info_20100312181719.htm

Original articles: http://www.wjgnet.com/1948-5204/g_info_20100312181919.htm

Brief articles: http://www.wjgnet.com/1948-5204/g_info_20100312182057.htm

Case report: http://www.wjgnet.com/1948-5204/g_info_20100312182207.htm

Letters to the editor: http://www.wjgnet.com/1948-5204/g_info_20100312182320.htm

Book reviews: http://www.wjgnet.com/1948-5204/g_info_20100312182437.htm

Guidelines: http://www.wjgnet.com/1948-5204/g_info_20100312182544.htm

SUBMISSION OF THE REVISED MANUSCRIPTS AFTER ACCEPTED

Please revise your article according to the revision policies of *WJGO*. The revised version including manuscript and high-resolution image figures (if any) should be copied on a floppy or compact disk. The author should send the revised manuscript, along with printed high-resolution color or black and white photos, copyright transfer letter, and responses to the reviewers by courier (such as EMS/DHL).

Editorial Office

World Journal of Gastrointestinal Oncology
Editorial Department: Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjgo@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-8538-1891
Fax: +86-10-8538-1893

Language evaluation
The language of a manuscript will be graded before it is sent for revision. (1) Grade A: priority publishing; (2) Grade B: minor language polishing; (3) Grade C: a great deal of language polishing needed; and (4) Grade D: rejected. Revised articles should reach Grade A or B.

Copyright assignment form
Please download a Copyright assignment form from http://www.wjgnet.com/1948-5204/g_info_20100312182928.htm.

Responses to reviewers
Please revise your article according to the comments/suggestions provided by the reviewers. The format for responses to the reviewers' comments can be found at: http://www.wjgnet.com/1948-5204/g_info_20100312182841.htm.

Proof of financial support
For paper supported by a foundation, authors should provide a copy of the document and serial number of the foundation.

Links to documents related to the manuscript
WJGO will be initiating a platform to promote dynamic interactions between the editors, peer reviewers, readers and authors. After a manuscript is published online, links to the PDF version of the submitted manuscript, the peer-reviewers' report and the revised manuscript will be put on-line. Readers can make comments on the peer reviewer's report, authors' responses to peer reviewers, and the revised manuscript. We hope that authors will benefit from this feedback and be able to revise the manuscript accordingly in a timely manner.

Science news releases
Authors of accepted manuscripts are suggested to write a science news item to promote their articles. The news will be released rapidly at EurekAlert/AAAS (http://www.eurekalert.org). The title for news items should be less than 90 characters; the summary should be less than 75 words; and main body less than 500 words. Science news items should be lawful, ethical, and strictly based on your original content with an attractive title and interesting pictures.

Publication fee
WJGO is an international, peer-reviewed, Open-Access, online journal. Articles published by this 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. Authors of accepted articles must pay a publication fee. The related standards are as follows. Publication fee: 1300 USD per article. Editorial, topic highlights, book reviews and letters to the editor are published free of charge.