“十三五”国家重点图书出版规划项目
上海高校服务国家重大战略出版工程

Translational Medicine Research

Series Editors: Zhu Chen · Xiaoming Shen
Saijuan Chen · Kerong Dai

Daxiang Cui et al *Editor*
崔大祥 等著

转化医学出版工程

陈 竺 沈晓明 总 主 编
陈赛娟 戴尅戎 执行总主编

Gastric Cancer Prewarning and Early Diagnosis System

胃癌预警和早期诊断系统

（英文版）

上海交通大学出版社
SHANGHAI JIAO TONG UNIVERSITY PRESS

“十三五”国家重点图书出版规划项目
国家科学技术学术著作出版基金资助
上海高校服务国家重大战略出版工程

Translational Medicine Research

Series Editors: Zhu Chen · Xiaoming Shen
Saijuan Chen · Kerong Dai

转化医学出版工程

陈　竺　沈晓明　总主编
陈赛娟　戴尅戎　执行总主编

Daxiang Cui et al Editor
崔大祥　等著

Gastric Cancer Prewarning and Early Diagnosis System

胃癌预警和早期诊断系统

（英文版）

上海交通大学出版社
SHANGHAI JIAO TONG UNIVERSITY PRESS

Springer

内容提要

本书系“转化医学出版工程：技术系列”之一，是关于纳米技术应用于胃癌早期检测系统的研究，主要内容包括胃癌标志物的筛选与鉴定；胃癌标志物超敏感特异性检测方法与诊疗器械研发；纳米粒子的制备与胃癌靶向成像与治疗一体化的多功能纳米探针的研制与应用；胃癌标志物快速检测传感器器件的研发与临床转化；胃癌循环血癌细胞的捕获与定量设备的研发；胃癌干细胞靶向成像与治疗的进展；胃癌细胞免疫治疗的进展；胃癌纳米探针的安全性评价与临床转化；原位胃癌分子分型的研究现状与指导靶向治疗药物的筛选；胃癌预警数据库和影像数据库的进展；胃癌预警与早期诊断系统临床转化的技术前景。本书是一本多学科交叉研究的结果总结，同时也对相关的研究进展进行了综述，对研究生、从事胃癌研究的人员以及临床医师都具有极高的参考价值与指导意义。

图书在版编目(CIP)数据

胃癌预警和早期诊断系统：英文/崔大祥等著；
—上海：上海交通大学出版社，2017
转化医学出版工程
ISBN 978-7-313-18136-7

Ⅰ.①胃… Ⅱ.①崔… Ⅲ.①胃癌—诊断—英文
Ⅳ.①R735.2

中国版本图书馆 CIP 数据核字(2017)第 227873 号

Not for sale outside the Mainland of China
(Not for sale in Hong Kong SAR, Macau SAR, and Taiwan,
and all countries except the Mainland of China)

胃癌预警和早期诊断系统(英文版)

著　　者：崔大祥等
出版发行：上海交通大学出版社　　地　　址：上海市番禺路 951 号
邮政编码：200030　　电　　话：021-64071208
出 版 人：谈　毅
印　　制：上海锦佳印刷有限公司　　经　　销：全国新华书店
开　　本：710mm×1000mm 1/16　　印　　张：23
字　　数：818 千字
版　　次：2017 年 11 月第 1 版　　印　　次：2017 年 11 月第 1 次印刷
书　　号：ISBN 978-7-313-18136-7/R
定　　价：268.00 元

版权所有　侵权必究
告读者：如发现本书有印装质量问题请与印刷厂质量科联系
联系电话：021-56401314

Translational Medicine Research

Volume 3

Series editors
Zhu Chen, Shanghai Jiaotong University, Shanghai, China
Xiaoming Shen, Shanghai Jiaotong University, Shanghai, China
Saijuan Chen, Shanghai Jiaotong University, Shanghai, China
Kerong Dai, Shanghai Jiaotong University, Shanghai, China

Aims and Scope

In collaboration with National Infrastructures for Translational Medicine (Shanghai), the largest translational medicine research center in China, the book series "Translational Medicine Research" offers a state-of-the-art resource for physicians and researchers alike who are interested in the rapidly evolving field of translational medicine. It features original and observational investigations in the broad fields of laboratory, clinical and public health research, providing practical and up-to-date information on significant research from all subspecialties of medicine and broadening readers' horizons, from bench to bed and bed to bench.

With a focus on global interdisciplinary academic collaboration, the series aims to expedite the translation of scientific discovery into new or improved standards of management and health outcomes practice.

Series Description

Translational medicine converts promising laboratory discoveries into clinical applications and elucidates clinical questions with the use of bench work, aiming to facilitate the prediction, prevention, diagnosis and treatment of diseases. The development of translational medicine will accelerate disease control and the process of finding solutions to key health problems. It is a multidisciplinary endeavor that integrates research from the medical sciences, basic sciences and social sciences, with the aim of optimizing patient care and preventive measures that may extend beyond health care services. Therefore, close and international collaboration between all parties involved is essential to the advancement of translational medicine.

To enhance the aforementioned international collaboration as well as to provide a forum for communication and cross-pollenation between basic, translational and clinical research practitioners from all relevant established and emerging disciplines, the book series "Translational Medicine Research" features original and observational investigations in the broad fields of laboratory, clinical and public health research, aiming to provide practical and up-to-date information on significant research from all subspecialties of medicine and to broaden readers' vision horizons, from bench to bed and bed to bench.

Produced in close collaboration with National Infrastructures for Translational Medicine (Shanghai), the largest translational medicine research center in China, the book series offers a state-of-the-art resource for physicians and researchers alike who are interested in the rapidly evolving field of translational medicine. Prof. Zhu Chen, the Editor-in-Chief of the series, is a hematologist at Shanghai Jiao Tong University, China's former Minister of Health, and chairman of the center's scientific advisory board.

More information about this series at http://www.springer.com/series/13024

此为试读,需要完整PDF请访问: www.ertongbook.com

Translational Medicine Research

Chief Editor

Zhu Chen Xiaoming Shen

Executive Editor

Saijuan Chen Kerong Dai

General Consultant

Dexiu Ma

Academic General Consultant

Zhenyi Wang

Academic Secretary

Yihuang Wang

Academic Committee

(Sort by alphabet order)

Xiuwu Bian

Institute of Pathology, Third Military Medical University

Guoqiang Chen

Shanghai Jiao Tong University School of Medicine

Yihan Chen

Shanghai East Hospital Affiliated to Tongji University

Zheng Feng

National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention

Junbo Ge

Tongji University; Shanghai Institute of Cardiovascular Disease, Fudan University

Yonghao Gui
Children's Hospital Affiliated to Fudan University

Zeguang Han
Chinese National Human Genome Center at Shanghai

Lin He
Bio-X Institutes, Shanghai Jiao Tong University

Hefeng Huang
International Peace Maternity & Child Health Hospital Affiliated to Shanghai Jiao Tong University School of Medicine

Yinghao Sun
The Second Military Medical University

Huiru Tang
School of Life Sciences, Fudan University

Hongyang Wang
ShanghaiEastern Hepatobiliary Surgery Hospital Affiliated to Second Military Medical University

Shengyue Wang
Chinese National Human Genome Center at Shanghai

Yu Wang
Chinese Center for Disease Control and Prevention

Dongqing Wei
School of Life Sciences and Biotechnology, Shanghai Jiao Tong University

Fan Wu
Shanghai Municipal Center for Disease Control & Prevention

Xuemin Xu
Med-X Institutes, Shanghai Jiao Tong University

Yixin Zeng
Department of Experimental Research, Sun Yat-Sen University Cancer Center

Chunhua Zhao
Chinese Academy of Medical Sciences & Peking Union Medical College

Yupei Zhao
Chinese Academy of Medical Sciences & Peking Union Medical College

Nanshan Zhong
The First Affiliated Hospital of Guangzhou Medical University

Series Foreword

Over the years, a chasm between biomedical researchers and the patients who may benefit from their discoveries has been opened. On one hand, millions of patients with diseases such as cancer are anxiously waiting for new remedies to save their lives. On the other hand, many exciting basic science discoveries do not have opportunities to find practical applications. Recently emerging translational medicine aims to tie basic research to clinical results and optimize both patient care and preventive measures.

Translational medicine converts promising laboratory discoveries into clinical applications and elucidates clinical questions with the use of bench work, aiming to facilitate prediction, prevention, diagnosis, and treatment of diseases. With the ultimate goal to develop more effective preventive/therapeutic approaches and improve clinical outcomes and health levels, translational medicine is therefore a people (patients and the general population as a whole)-oriented medical practice.

The past three decades have witnessed tremendous advances in China in the development of living conditions, food and nutrition, and the health care system. However, while the economy grows and society rapidly transforms, the health care system faces multiple problems. China bears a complex disease spectrum: On one hand, communicable diseases frequently seen in developing countries remain a heavy burden; on the other hand, chronic diseases commonly found in developed countries are also the leading causes of death and disability in China. The situation shows that the health care system in China is facing great challenges, and a state effort is needed to meet these challenges. Therefore China is deepening its reform to improve its people's welfare. The development of translational medicine will accelerate disease control and finding solutions for health problems.

Translational medicine is a multidisciplinary program that integrates research from the medical sciences, basic sciences, and social sciences, with the aim of optimizing patient care and preventive measures that may extend beyond health care services. Therefore, close collaboration in an international scale among all the parties is essential to the development of translational medicine.

To enhance the aforementioned international collaboration as well as to provide a forum for communication and cross-fertilization among basic, translational, and clinical research practitioners, we launch the book series "Translational Medicine Research". It features original and observational investigations in the broad fields of laboratory, clinical, and public health research, aiming to provide practical up-to-date information in significant research from all subspecialties of medicine and to broaden the readers' vision and horizon from bench to bed and bed to bench.

In close collaboration with National Infrastructures for Translational Medicine (Shanghai), the book series "Translational Medicine Research" serves as a state-of-the-art resource for physicians and translational medical researchers alike who are interested in the rapidly evolving field of translational medicine. As the Editor-in-Chief, I welcome all the researchers in related areas to report the latest bench-to-bedside researches in this series, so that the series can promote human health by accelerating the knowledge dissemination in global community.

Shanghai, China
May 2015

Zhu Chen

Preface

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death worldwide. It ranks number two among all malignant tumors in China. The gastric cancer prognosis is very poor with 5-year survivals below 24 %. How to realize gastric cancer prewarning and early diagnosis has become a key scientific problem. In 1998, my tutor Professor Chenzhi Su and Professor Xiaojun Yan in the Fourth Military Medical University put forward the concept of gastric cancer prewarning and early diagnosis system, designed its frame, obtained a key budget from the Department of Public Health of Shanxi Province, and then initiated its development.

Nanotechnology advances very fast. Nanomaterials and nanotechnology have integrated into gastric cancer theranostics, as a new emerging multidisciplinary frontier, exhibiting great potential in applications such as the prewarning and early diagnosis of gastric cancer. Under the support of the Chinese Nano Fundamental Research Project (2010CB933900), wrapping four key scientific problems such as gastric cancer biomarkers, ultrasensitive detection methods, nanoprobe-based qualitative and quantitative visualization, and biosafety of nanoprobes, our team finished some important works; it is very necessary to publish the book to introduce the advances associated with gastric cancer prewarning and early diagnosis system, which will be helpful to clinical doctors, undergraduate students, PhD students, and postgraduates.

This book contains a collection of major research accomplishments in the past decade or so in the area of specifically gastric cancer prewarning and early diagnosis system based on molecular biology, biological information, and nanotechnology in my team, mainly including screening gastric cancer biomarkers, developing ultrasensitive detection methods of gastric cancer biomarkers, designing and synthesizing molecular imaging probes for in vivo gastric cancer-targeted imaging and simultaneous therapy, gastric cancer operation boundary identification, metastasis lymph node tracking, gastric cancer stem cells identification and killing, and enhanced immuno-protection methods of gastric cancer patients, as well as clinical translation study and bioinformatic database.

This book includes 15 chapters. Chapter 1 exhibits the background of gastric cancer prewarning and early diagnosis system; Chaps. 2, 3, 4, 5, 6, and 7 exhibit

gastric cancer-associated biomarker screening and ultrasensitive detection methods; Chaps. 8, 9, and 10 exhibit established detection methods for gastric cancer biomarkers; Chaps. 11, 12, 13 and 14 exhibit multifunctional nanoprobes for theranostics of gastric cancer and biosafety assessment; and Chap. 15 exhibits part of the gastric cancer prewarning database and bioinformatic analysis method.

This book aims to improve the clinical translation of gastric cancer prewarning and early diagnosis system and to be the definitive reference book for scientists in the field of nanomedicine, theranostics, molecular imaging, and therapy. It is my hope that it can stimulate the interest of researchers and clinical doctors associated with these fields.

Finally, I would like to thank all members of my team and the staff of Springer for the support in making this book into reality.

Shanghai, China — Daxiang Cui

此为试读,需要完整PDF请访问: www.ertongbook.com

Contents

Chapter 1
Background of Gastric Cancer Prewarning and Early Diagnosis System

Daxiang Cui

Gastric cancer is the fourth most common cancer and the second leading cause of cancer-related death worldwide [1, 2]. In China, according to the latest cancer disease statistics, gastric cancer ranks as no. two in incidence and no. three in mortality rate of all malignant tumors [3]. The prognosis of gastric cancer is very poor, with 5-year survival less than 24 % [3, 4]. Early gastric cancer can be cured with surgery, while advanced gastric cancer often needs combined multidisciplinary therapy. Gastric cancer seems to be insensitive to current chemotherapy agents, a feature that may be closely related to the characteristics of stomach cancer stem cells [4, 5]. "Early gastric cancer" refers to in situ gastric cancer, which is located only in the gastric mucous membrane, and does not infiltrate into the thin submucosa. In China, the diagnosis rate of early gastric cancer is less than 20 %, whereas the diagnosis rates of early gastric cancer in Japan and South Korea have reached 30–50 % [6, 7]. Solving the problem of prewarning and early diagnosis of gastric cancer could not only save many patients with gastric cancer but also reduce the cost of treatment and even cure or significantly prolong the lifespan of patients.

1.1 Current Clinical Status of Gastric Cancer

The stomach is the body's most important digestive organ. The human stomach is located in the left hypochondrium, largely on the left side of the body's midline, with only a small portion on the right. The stomach is divided into four layers (from

D. Cui
Institute of Nano Biomedicine and Engineering, Shanghai Engineering Research Center for Intelligent Diagnosis and Treatment Instrument, National Center for Translational Medicine, Collaborative Innovational Center for System Biology, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai, 200240, P. R. China
e-mail: dxcui@sjtu.edu.cn

© Springer Science+Business Media B.V. and Shanghai Jiao Tong University Press, Shanghai 2017

D. Cui (ed.), *Gastric Cancer Prewarning and Early Diagnosis System*, Translational Medicine Research, DOI 10.1007/978-94-024-0951-2_1

the innermost to the outermost): mucosa, submucosa, muscularis, and serosa. Gastric cancer originates in the epithelial cells of the outermost layer, but it can occur in various parts of the stomach, such as the pyloric antrum (the most common area), the gastric cardia region, and, less likely, the gastric body. It may invade the stomach wall at different depths and breadths. With the naked eye or by endoscopy, gastric cancer can be observed to have a variety of forms, such as superficial, ulcerative, infiltrative, ulcerative carcinoma (cancer arising from chronic gastric ulcer), or mass. There are many histological classifications of cancer, such as adenocarcinoma (accounting for about 90%; including papillary adenocarcinoma, tubular adenocarcinoma, mucinous adenocarcinoma, and signet-ring-cell carcinoma), adeno-squamous cell carcinoma, squamous cell carcinoma, undifferentiated carcinoma, and carcinoid tumor [8, 9].

Gastric cancer is a malignant tumor; new cases of gastric cancer number more than 1 million each year globally, and worldwide more than 0.6 million deaths each year are due to the disease, with Japan, China, and South Korea having the highest incidence worldwide [10, 11, 31]. According to the 2012 China Cancer Registration Report, the incidence and mortality of gastric cancer rank as nos. two and three, respectively, among all malignant tumors in China [3]. In this report, the ratio of morbidity to mortality in both men and women was 2:1, and the incidence increased with age, being significantly higher among those aged 50 to 80 years; however, a younger trend has recently been noted, with the proportion of patients with gastric cancer aged 19 to 40 years increased from the originally reported 1.7% to the currently reported 3.3% [12]. An annual growth rate of 2.3% is predicted in the number of patients with gastric cancer in China [13, 14].

Gastric cancer rarely arises directly from the normal gastric mucosa; cancer formation shows a long process of evolution: from normal gastric mucosa to nonatrophic gastritis to atrophic gastritis to intestinal metaplasia to dysplasia to cancer. In gastric cancer science, this sequence of changes is universally recognized as the gastric cancer development model [15, 16]. The occurrence and progression of gastric cancer is a multifactorial process involving multiple gene interactions. It involves the evolution of a number of external and internal change factors. External environmental factors include *Helicobacter pylori* infection, dietary factors causing chronic inflammation, and other environmental factors; internal factors include the activation of oncogenes and inactivation of tumor suppressor genes, as well as the presence of some growth factors involved in DNA microsatellite instability caused by unlimited gastric epithelial cell proliferation [17].

As early as 1978, the World Health Organization (WHO) London Conference unified the concept of the pathological changes occurring in the body before gastric carcinoma occurs. Concepts of a precancerous state and precancerous lesions were defined. A precancerous state means a state associated with gastric diseases that pose a risk of gastric cancer, such as chronic atrophic gastritis, gastric polyps, gastric ulcers, gastritis, and other conditions. Precancerous lesions are a pathological concept, referring to pathological changes that are easily transformed into cancerous

tissue, including atypical hyperplasia or dysplasia and intestinal metaplasia. Chronic atrophic gastritis is considered to be a common precancerous condition, and gastric glandular atrophy and chronic inflammation are its main pathological features, accompanied by gastric dysplasia and intestinal metaplasia [18, 19]. Numerous studies indicate that there is a certain relationship between chronic atrophic gastritis and gastric cancer [20]. According to statistics, (67.8–92.3)% of gastric carcinoma specimens included chronic atrophic gastritis with intestinal metaplasia, while about 50% of gastric cancer specimens included precancerous diseases such as atrophic gastritis [21, 34]. In Japan, 4665 cases of healthy asymptomatic individuals were observed for a period of 7.7 years, and it was found that gastric cancer risk showed a gradual upward trend from chronic superficial gastritis, to chronic atrophic gastritis, and to severe atrophic gastritis with intestinal metaplasia; the probability of gastric cancer being caused by a low degree of dysplasia was 9%, and the probability of gastric cancer being caused by a high degree of dysplasia was 74% [22]. Inoue et al. [23] studied 5373 cases of chronic atrophic gastritis; the median follow-up time was 10 years, and 117 cases of cancer occurred. Moderate atrophic gastritis exhibited the highest risk of gastric cancer, with a risk factor of 2.22, and after a 4- to 6-year follow-up, the peak value for cancer risk was 5.0 [24]. Shigeto et al. [25] reported on 2859 healthy people (1011 males and 1848 females) followed-up at health examinations for 11 years, of whom ultimately 61 persons (33 men and 28 women) were found to have gastric cancer. The report also revealed that patients suffering from both chronic *H. pylori* infection and atrophic gastritis had a high risk of gastric cancer, while those patients suffering from chronic atrophic gastritis without *H. pylori* infection had the highest risk of gastric cancer [16, 26]. Chinese clinical studies also found that (1.2–7.1)% of patients with atrophic gastritis finally developed gastric cancer [27]. Diagnosis and treatment at an early stage is the most critical factor in improving the survival rate of gastric cancer. For patients with advanced gastric cancer and advanced metastasis, in whom repeated lymph node, blood, and peritoneal relapses occur, the prognosis is very poor; even in those who underwent radical surgery, the 5-year survival rate was only (5–20)% [3, 4]. After surgical resection and adjuvant therapy, patients with early gastric cancer have a 5-year survival rate of (90–95)% [3, 4].

In China, the current status of the diagnosis and treatment of gastric cancer presents "one high, three low" characteristics; namely, a high incidence of mortality, and low rates of early diagnosis, radical surgery, and 5-year survival [4]. In China, the early gastric cancer detection rate is only (10–20)% [16, 27], while in South Korea the rate is about 30% [28, 29] and in Japan the rate is up to (30–50)% [23, 30]. There is a considerable gap in the prevention and treatment of gastric cancer in China compared with the international advanced levels in Japan and South Korea, etc. It has been shown that nearly 80% of early gastric cancers have no symptoms, and the remaining 20% show only a few symptoms, such as mild ulcer-like dyspepsia, or similar nonspecific symptoms, which means that finding early gastric cancer in an asymptomatic population entails certain difficulties [16, 27, 29].

1.2 Main Diagnostic Methods for Gastric Cancer in the Clinical Setting

Currently, four methods are ordinarily used for the diagnosis of early gastric cancer: gastric endoscopy, imaging tools such as computed tomography (CT), pathological examination, and serological examination.

1.2.1 Endoscopy

Endoscopy (gastroscopy) is the most effective preferred method for early gastric cancer examination in the clinical setting. It can provide much information about gastric cancer lesions, such as their position, shape, and size; it has a wide field of vision and strong resolution; and it can be used to collect many samples for pathology examination, with high accuracy. The use of biopsy samples sprayed with pigment; brush cell slices; and smears can obviously improve the detection rate [35]. Without endoscopic examination, it is difficult to assess the level of tumor invasion and more difficult to assess the surrounding organs that have been invaded. However, gastroscopy is expensive and requires the operator to have certain experience; it may also cause pain and secondary damage. Patients with high blood pressure, blood diseases, and heart diseases are unfavorable candidates for gastroscopy.

1.2.2 Imaging Diagnosis

X-ray and CT are conventional methods for gastric cancer imaging examinations. CT imaging shows the normal stomach outline very clearly, in which the internal and external status of the stomach can be observed, as well as organs with remote metastasis; CT has a unique diagnostic effect for gastric cancers that grow inside the stomach wall or between the stomach layers, and it is superior to endoscopy and gastrointestinal angiography examination. CT is used for the assessment of lymph nodes; lymph nodes with a size of more than 1 cm can be diagnosed as lymph node metastases. Therefore, CT imaging improves the detection rate of gastric cancer, especially early gastric cancer, and it allows precise tumor staging by observing abnormal thickening of the gastric wall and changes in the gastric mucosa. Relevant data show that the sensitivity of CT detection of T1 and T2 gastric cancers was 75 %, and the concurrence rate of CT and clinical diagnosis was 68 %, while the sensitivity of CT detection of T3 and T4 gastric cancers was 98 %, and the concurrence rate of CT and clinical diagnoses was 88 %; these findings strongly suggest that CT has a high detection rate for the diagnosis of advanced gastric cancer, but for the diagnosis of early gastric cancer there is a low concurrence rate between CT detection and clinical diagnosis. Therefore, CT imaging is mainly used to determine whether distant lymph node metastasis (N phase) and liver metastasis (M phase) exist [32, 36].

此为试读,需要完整PDF请访问: www.ertongbook.com