

World Journal of *Gastrointestinal Oncology*

Monthly Volume 18 Number 2 February 15, 2026



World Journal of *Gastrointestinal Oncology*

Editorial Board

2026-2029

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
<https://www.wjgnet.com>

The *World Journal of Gastrointestinal Oncology* Editorial Board Members are composed of 72 distinguished experts active in the relevant field, distributed in 21 countries/regions, including China (18), Italy (9), United States (8), Japan (7), South Korea (5), Taiwan (4), Romania (3), Brazil (2), Türkiye (2), United Arab Emirates (2), United Kingdom (2), Canada (1), Russia (1), Saudi Arabia (1), Lithuania (1), Poland (1), Portugal (1), Egypt (1), Hungary (1), India (1), and Ireland (1).

Editor-in-Chief

Winnie Yeo, FRCP, FRCPE, MD, Professor, (E-mail: winnie@clo.cuhk.edu.hk) Department of Clinical Oncology, Prince of Wales Hospital, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong 999077, China

Senior Editorial Board

Monjur Ahmed, MD, Associate Professor, Department of Medicine, Division of Gastroenterology and Hepatology, Thomas Jefferson University, Philadelphia, PA 19107, United States

Florin Burada, MD, PhD, Professor, Department of Medical Genetics and Human Genomics Laboratory, Research Center of Gastroenterology and Hepatology, University of Medicine and Pharmacy of Craiova, Craiova 200349, Romania

Editorial Board

Wael M Abdel-Rahman, MD, PhD, Full Professor, Chairman, Department of Medical Laboratory Sciences, College of Health Sciences, University of Sharjah, Sharjah 27272, United Arab Emirates

Andreia Albuquerque, MD, PhD, Professor, Department of Medicine and Biomedical Sciences, Faculty of Medicine of the University of Porto, No. 150 Av. Fernando Pessoa, Porto 4420-096S, Portugal

Paolo Aurello, MD, PhD, Assistant Professor, Professor, Department of General Surgery, Sapienza University of Rome, Rome 00162, Italy

Samy Azer, FACC, MD, PhD, Professor, Department of Medical Education, King Saud University College of Medicine, Riyadh 11461, Saudi Arabia

Asfar Sohail Azmi, PhD, Associate Professor, Director, Department of Oncology, Wayne State University School of Medicine, Karmanos Cancer Institute, Detroit, MI 48201, United States

Simona Maria Bataga, PhD, Professor, AGAF, Department of Gastroenterology, University of Medicine, Pharmacy, Science and Technology, GE Palade, Targu-Mures 540085, Romania

Rossana Berardi, MD, PhD, Director, Full Professor, Medical Oncology, Università Politecnica delle Marche, Ancona 60126, Italy

Zhi-Fei Cao, MD, PhD, Assistant Professor, Research Assistant Professor, Department of Pathology, The Second Affiliated Hospital of Soochow University, Suzhou 215004, Jiangsu Province, China

Gabriele Capurso, MD, PhD, Pancreato-Biliary Endoscopy and Endosonography Division, Pancreas Translational and Clinical Research Center, IRCCS San Raffaele Scientific Institute, Milano 20132, Italy

José Carvalheira, MD, PhD, Associate Professor, Department of Anesthesiology, Oncology and Radiology, School of Medical Sciences, University of Campinas, Campinas, São Paulo 13083, Brazil

Claudio Casella, PhD, Assistant Professor, Scientific Sector MED/18 ("General Surgery"), University of Brescia-School of Medicine, Brescia I-25123, Italy

Soo-Cheon Chae, PhD, Professor, Department of Pathology, School of Medicine, Wonkwang University, Chonbuk 54538, South Korea

Xin-Zu Chen, PhD, MD, Professor, Gastric Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China; Ya'an Cancer Prevention and Control Center, Ya'an Key Laboratory for High Altitude Medicine, Ya'an People's Hospital-West China Ya'an Hospital, Sichuan University, Ya'an 625499, Sichuan Province, China

Hao Chi, MD, Assistant Professor, Department of Clinical Medicine, Clinical Medical College, Southwest Medical University, Luzhou 646000, Sichuan Province, China

Zilvinas Dambrauskas, MD, PhD, Professor, Department of Surgery and Institute for Digestive System Research, Lithuanian University of Health Sciences, Kaunas 50161, Lithuania

Jing-Yu Deng, MD, PhD, Professor, Department of Gastroenterology, Tianjin Medical University Cancer Hospital, City Key Laboratory of Tianjin Cancer Center and National Clinical Research Center for Cancer, Tianjin 300060, China

Hiroshi Doi, MD, PhD, Assistant Professor, Department of Radiation Oncology, Kindai University Faculty of Medicine, Osaka 589-8511, Japan

Yi Dong, PhD, Professor, Department of Ultrasound, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200092, China

Renato Borges Fagundes, MD, PhD, Full Professor, Gastroenterology Department of Hospital Universitário de Santa Maria, Universidade Federal de Santa Maria, Porto Alegre, RS 90480200, Brazil

Yao-Hui Gao, PhD, Additional Professor, Department of Pathology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China

Eun Jeong Gong, MD, PhD, Associate Professor, Department of Internal Medicine, Hallym University College of Medicine, Chuncheon 24253, South Korea; Institute for Liver and Digestive Diseases, Hallym University, Chuncheon 24253, South Korea; Institute of New Frontier Research, Hallym University College of Medicine, Chuncheon 24252, South Korea

Travis Edward Grotz, MD, Assistant Professor, Department of Surgery, Mayo Clinic, Rochester, MN 55905, United States

Ming-Zhou Guo, MD, PhD, Professor, Department of Gastroenterology and Hepatology, The First Medical Center, Chinese PLA General Hospital, Beijing 100853, China; National Key Laboratory of Kidney Diseases, The First Medical Center, Chinese PLA General Hospital, Beijing 100853, China

Tomohide Hori, FACS, MD, PhD, Director, Department of Gastroenterology and Hepatology, Nagai Hospital, Tsu, Mie 514-8508, Japan

Jun-Te Hsu, MD, Director, Professor, Department of Surgery, Chang Gung Memorial Hospital at Linkou, Taoyuan 333, Taiwan

Keun-Yeong Jeong, PhD, Assistant Professor, Head Office, Research Center, PearlsInMires, No. 150 Yeongdeungpo-ro, Yeongdeungpo-gu, Seoul 07292, South Korea

Lei Jiang, PhD, Professor, Central Lab, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou 325000, Zhejiang Province, China

Yan Jiao, PhD, Assistant Professor, Department of Hepatobiliary and Pancreatic Surgery, General Surgery Center, First Hospital of Jilin University, Changchun 130021, Jilin Province, China

Freimut Dankwart Eberhard Juengling, MD, PhD, Full Professor, Department of Oncology, Cross Cancer Institute, Edmonton, AB T6G 1Z2, Canada

Ki Mun Kang, MD, PhD, Professor, Department of Radiation Oncology, Gyeongsang National University College of Medicine, Jinju 52727, South Korea

Hiroshi Kishikawa, MD, PhD, Associate Professor, Department of Gastroenterology, Ichikawa General Hospital, Tokyo Dental College, Chiba 272-8513, Japan

Małgorzata Kujawska, PhD, Professor, Department of Toxicology, Poznan University of Medical Sciences, No. 3 Rokietnicka Street, Poznan 60-806, Poland

Sung-Hsin Kuo, MD, PhD, Professor, Department of Oncology, National Taiwan University Hospital, Taipei 100, Taiwan

Wey-Ran Lin, AGAF, MD, PhD, Professor, Department of Gastroenterology and Hepatology, Linkou Chang Gung Memorial Hospital, Taoyuan 333, Taiwan

Li-Yan Liu, Professor, PhD, Department of Nutrition and Food Hygiene, Key Laboratory of Precision Nutrition and Health of Ministry of Education, Harbin Medical University, No. 157 Baojian Road, Harbin 150086, Heilongjiang Province, China

Maria Anatolyevna Livzan, MD, Professor, Department of Faculty Therapy, Federal State Budgetary Educational Institution of Higher Education, Omsk State Medical University, Ministry of Healthcare of the Russian Federation, No. 12 Lenin Street, Omsk 644099, Russia

Yun-Xia Lu, PhD, MD, Associate Professor, Department of Population Health and Disease Prevention, Joe C. Wen School of Population and Public Health, Henry Samueli College of Health Sciences, University of California, Irvine, CA 92697, United States

Claudio Luchini, MD, PhD, Associate Professor, Department of Diagnostics and Public Health, University and Hospital Trust Verona, Verona 37134, Italy

Luigi Marano, MD, PhD, Associate Professor, Department of Medicine, Surgery, and Neurosciences, University of Siena, Siena 53100, Italy

Sara Massironi, MD, PhD, Assistant Professor, Department of Medicine and Surgery, Vita-Salute San Raffaele University, Milan 20132, Italy

Tamás Micsik, MD, PhD, Assistant Professor, 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest h-1085, Hungary

Salem Youssef Mohamed, MD, Professor, Department of Internal Medicine, Zagazig University, Zagazig 44516, Egypt

Yoshifumi Nakayama, MD, PhD, Professor, Department of Surgery, Kitakyushu General Hospital, Kitakyushu 802-8517, Japan

Akihiko Oka, MD, PhD, Assistant Professor, Department of Internal Medicine II, Shimane University Faculty of Medicine, Izumo 693-8501, Japan

Colm A O'Morain, AGAF, FACC, FRCP, MD, Full Professor, Health Sciences, Royal College of Physicians of Ireland, Dublin 18, Ireland

Gaetano Piccolo, MD, PhD, Professor, Department of Health Sciences, University of Milan, San Paolo Hospital, Via Antonio di Rudini 8, Milano 20142, Italy

Manmeet Rawat, Assistant Professor, PhD, Division of Gastroenterology and Hepatology, Department of Medicine, The Penn State University College of Medicine, Hershey, PA 17033, United States

Sezer Saglam, MD, Full Professor, Medical Oncology, Demiroglu Bilim University, Gayrettepe Florence Nighthale Hospital, Istanbul, Besiktas 34349, Türkiye

Shaji Sebastian, FRCP (C), MD, Professor, Hull York Medical School, Hull and East Yorkshire NHS Trust, Hull HU3 2JZ, United Kingdom

Andrada Seicean, MD, PhD, Professor, Regional Institute of Gastroenterology and Hepatology Cluj-Napoca, University of Medicine and Pharmacy, Cluj-Napoca 400192, Romania

Durairaj Sekar, PhD, Full Professor, Professor, Biomedical Research Unit, Saveetha University, Chennai 600077, India

Santosh Shenoy, FACS, MD, Professor, Department of General and Colorectal Surgery, KCVA and University of Missouri at Kansas City, Missouri, MO 64128, United States

Jiaqi Shi, MD, PhD, Professor, Department of Pathology, University of Michigan, Ann Arbor, MI 48109, United States

Lele Song, MD, PhD, Associate Professor, Department of Radiotherapy, The Eighth Medical Center of the Chinese PLA General Hospital, Beijing 100091, China

Caecilia Hapsari Cериapuri Sukowati, Senior Researcher, Liver Cancer Unit, Italian Liver Foundation NPO-Fondazione Italiana Fegato ONLUS, AREA Science Park Basovizza-Bldg Q, SS14 Km 163.5, Trieste 34149, Italy; Eijkman Research Center for Molecular Biology, National Research and Innovation Agency of the Republic of Indonesia, B.J. Habibie Building, No. 8 Jl. M.H. Thamrin, Jakarta Pusat 10340, Indonesia

Yu Sunakawa, MD, PhD, Associate Professor, Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Kanagawa 216-8511, Japan

Wen-Wei Sung, MD, PhD, Associate Professor, Department of Urology, School of Medicine, Chung Shan Medical University Hospital, Taichung 40201, Taiwan

Iman M Talaat, MD, PhD, Full Professor, Department of Clinical Sciences, College of Medicine, University of Sharjah, Sharjah 27272, United Arab Emirates

Gao Tan, PhD, Professor, Guangdong Provincial Key Laboratory of Gastroenterology, Institute of Gastroenterology of Guangdong Province, Department of Gastroenterology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, Guangdong Province, China

Shinji Tanaka, FACS, MD, PhD, Professor, Department of Molecular Oncology, Tokyo Medical and Dental University, Tokyo 113-8519, Japan

Mesut Tez, MD, Professor, Department of Surgery, Ankara Numune Training and Research Hospital, Ankara 06100, Türkiye

Yan-Tao Tian, MD, PhD, Professor, Chief Physician, Department of Pancreatic and Gastric Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Esther Una Cidon, MD, PhD, Department of Medical Oncology, Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Bournemouth BH7 7DW, United Kingdom

Chang-Jie Wu, PhD, Associate Professor, Guangdong Provincial Key Laboratory of Gastroenterology, Department of Gastroenterology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, Guangdong Province, China

Xiang Xue, Associate Professor, Department of Biochemistry and Molecular Biology, University of New Mexico, Albuquerque, NM 87131, United States

Ru-Yi Xue, MD, PhD, Associate Chief Physician, Clinical Assistant Professor (Honorary), Department of Gastroenterology and Hepatology, Zhongshan Hospital, Shanghai Institute of Liver Disease, Fudan University, Shanghai 200032, China

Yong Sik Yoon, MD, PhD, Professor, Colon and Rectal Surgery, Asan Medical Center and University of Ulsan College of Medicine, Seoul 05505, South Korea

Jia-Liang Zhang, Assistant Professor, MD, State Key Laboratory of Oncology in South China and Guangdong Provincial Clinical Research Center for Cancer, Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-sen University Cancer Center, No. 651 Dongfeng Road East, Guangzhou 510060, Guangdong Province, China

Hong Zhu, Associate Chief Physician, Associate Professor, Department of Abdominal Cancer, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

EDITORIAL

Zhao ZX. Radiomics-based model for predicting neoadjuvant therapy response in esophageal cancer: Limitations and suggestions. *World J Gastrointest Oncol* 2026; 18(2): 114981 [DOI: [10.4251/wjgo.v18.i2.114981](https://doi.org/10.4251/wjgo.v18.i2.114981)]

Karmakar R, Kandalkar A, Mukundan A. Total neoadjuvant therapy in rectal cancer: Challenging traditions without compromising surgical safety. *World J Gastrointest Oncol* 2026; 18(2): 115507 [DOI: [10.4251/wjgo.v18.i2.115507](https://doi.org/10.4251/wjgo.v18.i2.115507)]

Arun O, Arun F. Does anesthesia choice shape oncologic destiny in gastric cancer surgery? *World J Gastrointest Oncol* 2026; 18(2): 115944 [DOI: [10.4251/wjgo.v18.i2.115944](https://doi.org/10.4251/wjgo.v18.i2.115944)]

REVIEW

Yang RR, Yan YR, Li YF. Recent advances in spasmolytic polypeptide expressing metaplasia research. *World J Gastrointest Oncol* 2026; 18(2): 113995 [DOI: [10.4251/wjgo.v18.i2.113995](https://doi.org/10.4251/wjgo.v18.i2.113995)]

Jing LB, Liu J, Yang ZH, Yang FF, Wang DG, Li YM. Metallic elements and their molecular roles in gastric cancer: Pathogenic mechanisms and therapeutic implications. *World J Gastrointest Oncol* 2026; 18(2): 114351 [DOI: [10.4251/wjgo.v18.i2.114351](https://doi.org/10.4251/wjgo.v18.i2.114351)]

MINIREVIEWS

Dutta AK, Rao NV, Bharadwaj PK, Benny S. Frequency and characteristics of synchronous gastric cancers: Need for improved awareness and better detection. *World J Gastrointest Oncol* 2026; 18(2): 113508 [DOI: [10.4251/wjgo.v18.i2.113508](https://doi.org/10.4251/wjgo.v18.i2.113508)]

Sehgal T, Joshi T, Chowdhary R, Goyal O, Kalra S, Goyal R, Taranikanti V, Vuthaluru AR, Goyal MK. Deep learning in lower gastrointestinal cancer detection: Advances in endoscopic, radiologic, and histopathologic diagnostics. *World J Gastrointest Oncol* 2026; 18(2): 115974 [DOI: [10.4251/wjgo.v18.i2.115974](https://doi.org/10.4251/wjgo.v18.i2.115974)]

Li WM, Jiao Y, Liu SQ, Wang CX, He M. Ethnic genomic diversity in esophageal squamous cell carcinoma. *World J Gastrointest Oncol* 2026; 18(2): 116345 [DOI: [10.4251/wjgo.v18.i2.116345](https://doi.org/10.4251/wjgo.v18.i2.116345)]

ORIGINAL ARTICLE**Retrospective Cohort Study**

Wang YR, Wang JQ, Chen XJ, Yan Y, Zhang Y, Li MY, Wang W, Fan TY, Jiao PF, Zhou CF. Efficacy and safety of integrated Chinese and Western medicine in advanced pancreatic cancer: A double-center retrospective cohort study. *World J Gastrointest Oncol* 2026; 18(2): 114690 [DOI: [10.4251/wjgo.v18.i2.114690](https://doi.org/10.4251/wjgo.v18.i2.114690)]

Retrospective Study

Abbas Z, Gazder DP, Hyder Z, Qadeer MA, Abbas M. Serum protein induced by vitamin K absence or antagonist-II predicts aggressive tumor biology in alpha-fetoprotein-normal hepatocellular carcinoma. *World J Gastrointest Oncol* 2026; 18(2): 113673 [DOI: [10.4251/wjgo.v18.i2.113673](https://doi.org/10.4251/wjgo.v18.i2.113673)]

Cao H, Han JL, Wu H, Si SP, Ding LJ, Ji L, Zhang HZ, Yin J, Zhou ZY, Zhang YN, Lv ZF, Tian WY, Zhan Q, Wang H, An FM. Risk prediction for chronic atrophic gastritis using a random forest model: A multicenter study. *World J Gastrointest Oncol* 2026; 18(2): 113959 [DOI: 10.4251/wjgo.v18.i2.113959]

Chen HZ, Zhang P, Ma J. Computed tomography with carcinoembryonic antigen and carbohydrate antigen 19-9 in diagnosing lymph node metastasis of early gastric cancer. *World J Gastrointest Oncol* 2026; 18(2): 114066 [DOI: 10.4251/wjgo.v18.i2.114066]

Luo ZC, Guo HY, Tang X, Chen XR, Zhang CY, Cui YT, Zuo J, Li HR, Hou XM, Chen H, Song SB, Wang XF. Predicting the magnitude of risk for non-curative endoscopic submucosal dissection in superficial esophageal cancer using explainable artificial intelligence. *World J Gastrointest Oncol* 2026; 18(2): 114782 [DOI: 10.4251/wjgo.v18.i2.114782]

Huang L, Li JT, Zhou WJ, Wu QF. Endoscopic vs laparoscopic resection for gastric gastrointestinal stromal tumors: Oncological outcomes. *World J Gastrointest Oncol* 2026; 18(2): 115199 [DOI: 10.4251/wjgo.v18.i2.115199]

Qi XS, Xie J, Liu NL, Yang L. Relationship between preoperative modified frailty index, immune-inflammation index, and outcomes of colorectal cancer surgery in older patients. *World J Gastrointest Oncol* 2026; 18(2): 115224 [DOI: 10.4251/wjgo.v18.i2.115224]

Zhong WT, Ding SK, Li RY, Liu CY, Huang HY, Yu JC. Clinical value of geriatric nutritional risk index and pan-immune-inflammation value in locally advanced gastric cancer receiving neoadjuvant chemotherapy. *World J Gastrointest Oncol* 2026; 18(2): 115387 [DOI: 10.4251/wjgo.v18.i2.115387]

Mu XD, Ji DX, Kang DQ. Application value of multiphase contrast-enhanced computed tomography radiomics in preoperative evaluation of peritoneal metastasis in gastric cancer. *World J Gastrointest Oncol* 2026; 18(2): 115404 [DOI: 10.4251/wjgo.v18.i2.115404]

Lu YY, Chen P, Lu Y. Clinical characteristics of programmed death-1 inhibitors for older patients with advanced pancreatic cancer. *World J Gastrointest Oncol* 2026; 18(2): 115562 [DOI: 10.4251/wjgo.v18.i2.115562]

Clinical Trials Study

Qin HY, Li Z, Cong PW, Mi D, Li FZ, Hu X, Li GX. Clinical efficacy of Fuzheng Jiedu Xiaoyong granules in advanced colorectal cancer (spleen deficiency and stasis toxin syndrome). *World J Gastrointest Oncol* 2026; 18(2): 113922 [DOI: 10.4251/wjgo.v18.i2.113922]

Observational Study

Zhao XL, Chen WY, Liu YM, Danzeng SL, Pingcuo QZ, Yu Z, Chen HD, Ciren YJ, Wu D. Detection rate and risk factors of colorectal adenoma in high-altitude population: A cross-sectional study. *World J Gastrointest Oncol* 2026; 18(2): 116336 [DOI: 10.4251/wjgo.v18.i2.116336]

Basic Study

Liu K, Zhang X, Li FZ, Zheng PY, Mi Y. Taurine suppresses gastric intestinal metaplasia in patient-derived organoids and *Atp4a*^{-/-} mice. *World J Gastrointest Oncol* 2026; 18(2): 114161 [DOI: 10.4251/wjgo.v18.i2.114161]

Lin X, Lin GF, Gu FT, Li YL. Increasing expression of presenilin 1, β -catenin, and p-PTEN and its regulatory roles on cell invasion in gastric cancer. *World J Gastrointest Oncol* 2026; 18(2): 115689 [DOI: 10.4251/wjgo.v18.i2.115689]

SYSTEMATIC REVIEWS

Akbulut S, Colak C. Pioneering efficient deep learning architectures for enhanced hepatocellular carcinoma prediction and clinical translation. *World J Gastrointest Oncol* 2026; 18(2): 113870 [DOI: 10.4251/wjgo.v18.i2.113870]

META-ANALYSIS

Xiang MY, Tuo ZM, Sa XK, Wang P, Bian JW, Zhang XM. Impact of liver metastasis on the efficacy of immune checkpoint inhibitors for advanced colorectal cancer. *World J Gastrointest Oncol* 2026; 18(2): 115515 [DOI: [10.4251/wjgo.v18.i2.115515](https://doi.org/10.4251/wjgo.v18.i2.115515)]

CASE REPORT

Zhang Y, Li ZX, Ma DY, Liu F. Solitary esophageal metastasis ten years after curative resection of stage I rectal adenocarcinoma: A case report. *World J Gastrointest Oncol* 2026; 18(2): 113494 [DOI: [10.4251/wjgo.v18.i2.113494](https://doi.org/10.4251/wjgo.v18.i2.113494)]

Li JL, Cheng C, Zhang P, Fan J, Zhang L, Zhu LR, Tao KX, Cai M. Rectal follicular thyroid-like carcinoma: A case report and review of literature. *World J Gastrointest Oncol* 2026; 18(2): 115179 [DOI: [10.4251/wjgo.v18.i2.115179](https://doi.org/10.4251/wjgo.v18.i2.115179)]

LETTER TO THE EDITOR

Ismaili N. Shifting paradigm in locally advanced resectable gastric and gastroesophageal junction cancers. *World J Gastrointest Oncol* 2026; 18(2): 113150 [DOI: [10.4251/wjgo.v18.i2.113150](https://doi.org/10.4251/wjgo.v18.i2.113150)]

Chen YX, Zhang YH, Mo SJ. Role of microRNA-136 in *Helicobacter pylori*-induced early-stage gastric cancer: Mechanistic insights and future directions. *World J Gastrointest Oncol* 2026; 18(2): 114163 [DOI: [10.4251/wjgo.v18.i2.114163](https://doi.org/10.4251/wjgo.v18.i2.114163)]

Zhang TT, Yao J, Zhang HM. Microbiota-metabolite signatures in metastatic colorectal cancer: Promise, pitfalls, and the path forward. *World J Gastrointest Oncol* 2026; 18(2): 115010 [DOI: [10.4251/wjgo.v18.i2.115010](https://doi.org/10.4251/wjgo.v18.i2.115010)]

Nayak A, Sahoo G, Nishank SS. Advancing precision medicine in human epidermal growth factor receptor 2 negative gastric cancer: Insights from a novel nomogram for immunochemotherapy prognosis. *World J Gastrointest Oncol* 2026; 18(2): 115401 [DOI: [10.4251/wjgo.v18.i2.115401](https://doi.org/10.4251/wjgo.v18.i2.115401)]

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Simona Maria Bataga, PhD, Professor, AGAF, Department of Gastroenterology, University of Medicine, Pharmacy, Science and Technology, GE Palade, Targu-Mures 540085, Romania. simonabataga@yahoo.com

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

INDEXING/ABSTRACTING

The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2025 edition of Journal Citation Reports® cites the 2024 journal impact factor (JIF) for *WJGO* as 2.5; JIF without journal self cites: 2.4; 5-year JIF: 2.7; JIF Rank: 68/147 in gastroenterology and hepatology; JIF Quartile: Q2; and 5-year JIF Quartile: Q3. The *WJGO*'s CiteScore for 2024 is 3.3 and Scopus CiteScore rank 2024: Gastroenterology is 89/173; Oncology is 235/415.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Si Zhao*; Production Department Director: *Xiang Li*; Cover Editor: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastrointestinal Oncology

ISSN

ISSN 1948-5204 (online)

LAUNCH DATE

February 15, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Monjur Ahmed

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-5204/editorialboard.htm>

PUBLICATION DATE

February 15, 2026

COPYRIGHT

© 2026 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Recent advances in spasmolytic polypeptide expressing metaplasia research

Rui-Rui Yang, Ya-Ru Yan, Yu-Feng Li

Specialty type: Oncology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade C

Novelty: Grade C, Grade C

Creativity or Innovation: Grade C, Grade C

Scientific Significance: Grade C, Grade D

P-Reviewer: Feng ZJ, Postdoctoral Fellow, China; Sevinç B, MD, Associate Professor, Türkiye

Received: September 9, 2025

Revised: October 23, 2025

Accepted: December 10, 2025

Published online: February 15, 2026

Processing time: 147 Days and 13.1 Hours



Rui-Rui Yang, First Clinical School, Liaoning University of Chinese Medicine, Shenyang 110847, Liaoning Province, China

Rui-Rui Yang, Yu-Feng Li, Department of Gastroenterology, Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, Shenyang 110847, Liaoning Province, China

Ya-Ru Yan, Heilongjiang Provincial Academy of Traditional Chinese Medicine, Harbin 150036, Heilongjiang Province, China

Co-first authors: Rui-Rui Yang and Ya-Ru Yan.

Corresponding author: Yu-Feng Li, Chief Physician, Professor, Department of Gastroenterology, Affiliated Hospital of Liaoning University of Traditional Chinese Medicine, No. 33 Beiling Street, Huanggu District, Shenyang 110847, Liaoning Province, China.
3278086072@qq.com

Abstract

Gastric cancer remains a leading cause of global cancer mortality, with limited advances in its prevention and treatment owing to an incomplete understanding of its pathogenesis. Among the key precancerous lesions, spasmolytic polypeptide-expressing metaplasia has emerged as a critical driver in gastric carcinogenesis. This review summarizes the recent advances in the mechanistic roles of spasmolytic polypeptide-expressing metaplasia in gastric mucosal diseases. By elucidating these pathways, this review sought to provide novel insights that could inform future strategies for early intervention and prevention of gastric cancer.

Key Words: Gastric adenocarcinoma; Spasmolytic polypeptide-expressing metaplasia; Signaling pathway; Research progress; Pathogenesis

©The Author(s) 2026. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Gastric cancer is one of the most common cancers worldwide, with exceptionally high morbidity and fatality rates. A thorough investigation of the pathophysiology of spasmodic polypeptide-expressing metaplasia (SPEM) is required. SPEM serves as a critical nexus between mucosal repair and gastric carcinogenesis and is a valuable target for early detection and intervention. To gain a deeper understanding of SPEM, this review summarizes its recent mechanistic roles in gastric mucosal diseases. By elucidating these mechanisms, this review aims to provide deeper insights into the research and prevention of SPEM-related diseases.

Citation: Yang RR, Yan YR, Li YF. Recent advances in spasmodic polypeptide expressing metaplasia research. *World J Gastrointest Oncol* 2026; 18(2): 113995

URL: <https://www.wjgnet.com/1948-5204/full/v18/i2/113995.htm>

DOI: <https://dx.doi.org/10.4251/wjgo.v18.i2.113995>

INTRODUCTION

Spasmodic polypeptide-expressing metaplasia (SPEM) is an adaptive metaplastic cell lineage that develops in the gastric mucosa in response to injury. Although traditionally regarded as a reparative program, its strong association with gastric cancer development has led to SPEM redefinition as a critical precursor lesion and an important target for its prevention. Gastric cancer is a major global health burden and ranks as the fifth most common malignancy worldwide in terms of both incidence and mortality[1]. Its development often follows the classic Correa cascade, a multistep progression from normal gastric mucosa to invasive carcinoma through chronic gastritis, atrophic gastritis, intestinal metaplasia (IM), and dysplasia stages[2]. Throughout this process, persistent atrophy and inflammation drive the development of metaplastic lesions such as SPEM and IM, which are recognized as precancerous conditions. Consequently, SPEM is regarded as a key target for the prevention and control of gastric cancer.

The stomach epithelium exhibits considerable self-renewal capacity and cellular plasticity, enabling periodic differentiation and dedifferentiation of gastric epithelial cells, a property that inherently increases the susceptibility to carcinogenesis[3]. Under acute or chronic inflammatory conditions, parietal cell loss from the normal gastric mucosa marks the onset of oxyntic atrophy, which is a prerequisite for the emergence of SPEM[4]. Beyond parietal cell loss, depletion of chief cells has also been identified as an initiating factor in gastric mucosal injury[5,6].

SPEM concept emerged from observations of aberrant epithelial lineages in *Helicobacter pylori* (*H. pylori*)-infected mice [7], and is now recognized as an adaptive, repair-oriented cellular conversion. SPEM is characterized by the expression of trefoil factor 2 (TFF2) and mucin 6 (MUC6)[8,9]. In contrast, IM is generally regarded as the outcome of transdifferentiation toward an intestinal phenotype, featuring the presence of MUC-containing goblet cells, Paneth cells, and absorptive enterocytes, along with TFF3 and MUC2 expression[10]. SPEM is typically located deep in the fundic gland. In contrast, IM is present in the gland lumen, and evidence suggests that IM likely evolves from SPEM[4,11]. Consequently, SPEM and IM detection in clinical specimens is crucial for risk stratification and early intervention in gastric cancer.

MECHANISM OF SPEM AND ITS ORIGIN

The cellular origin of SPEM, which is central to understanding its initiation, is the subject of active investigation and debate. While the predominant model centers on the transdifferentiation of mature chief cells, emerging evidence suggests alternative cellular sources that highlight the plasticity of the gastric epithelium. Cell differentiation is the developmental mechanism by which a cohort of multipotent progenitors gives rise to diverse specialized cell lineages, each with unique morphological and functional properties[3]. In the stomach, tissue repair after injury involves reprogramming fully differentiated cells back into a less-differentiated proliferative state to replenish lost cells. Pathologists refer to this stereotypical cycle of cellular phenotypic changes as paligenosis.

Chief cell transdifferentiation via paligenosis

The cellular origin of SPEM has not been fully determined; however, the most widely accepted explanation is that it arises from the transdifferentiation of mature chief cells[12], also known as pyloric metaplasia, which is histologically defined by the luminal proliferation of MUC5AC-positive cells, concurrent with parietal cell loss and replacement of chief cells by basally emerging SPEM cells[7]. Through an evolutionarily conserved process termed “paligenosis”, mature gastric chief cells can be reprogrammed, re-enter the cell cycle, and transform into SPEM cells (Figure 1)[13].

A preliminary exploration of the process of chief cell transdifferentiation into SPEM cells has been reported. This process begins with the dedifferentiation of chief cells, which is marked by the key molecular event of muscle, intestine, stomach expression 1 (MIST1) downregulation[14]. This process begins with the disruption of normal cellular morphology *via* the activation of the lysosomal and autophagic pathways. It has been proposed that a related process, termed “cathartocytosis”, may occur in parallel with autophagy. Although mechanistically distinct, cathartocytosis enables the cell to rapidly expel excess material, such as endoplasmic reticulum membranes and secretory granule contents[15].

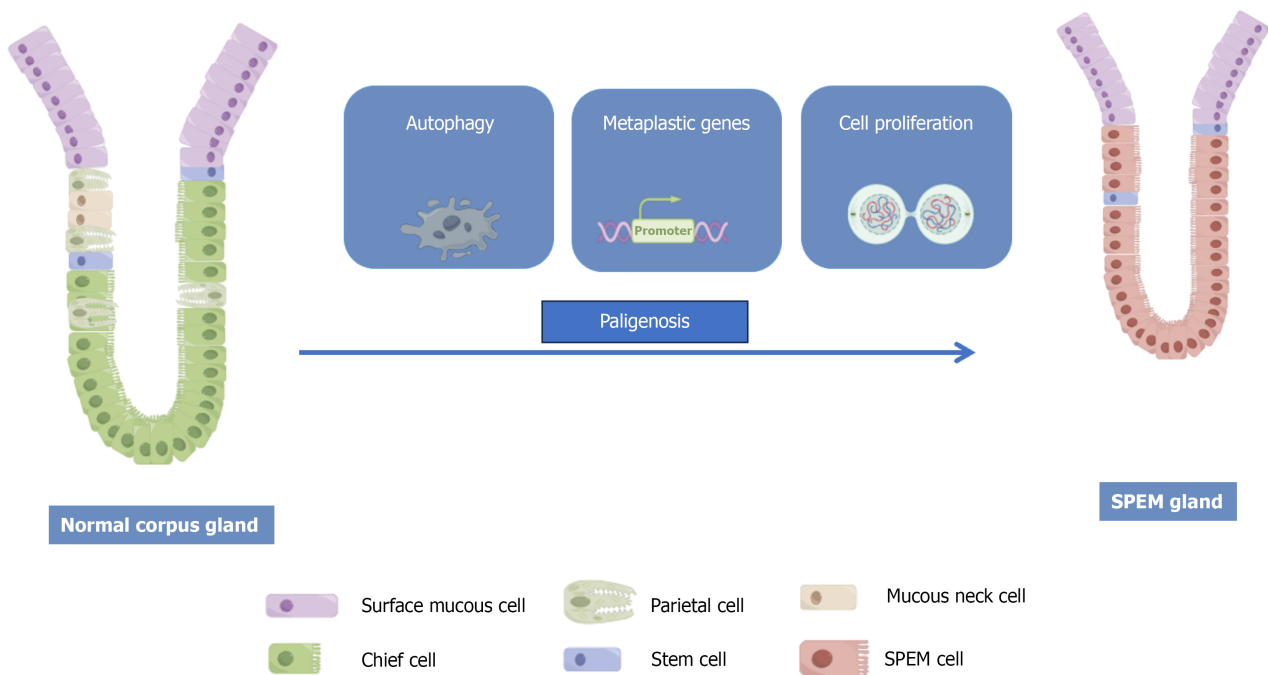


Figure 1 Spasmolytic polypeptide-expressing metaplasia process in “paligenosis”. SPEM: Spasmolytic polypeptide-expressing metaplasia.

In the early stages of pathogenesis, activating transcription factor 3 is upregulated, which induces autophagy and lysosomal activity to dismantle the characteristic structures of differentiated chief cells[16]. Chief cell reprogramming is initiated by sulforaphane (Sfn)[17] and is accompanied by MIST1 downregulation[14] and upregulation of aquaporin 5 (AQP5)[18] and SRY-Box transcription factor 9 (SOX9)[19]. Notably, SFN loss in chief cells abrogates SOX9 expression. SOX9 itself is also known to promote metaplasia in Barrett’s esophagus[20].

In the later stages, transdifferentiated cells begin to produce cytoplasmic granules expressing TFF2 or MUC6, a process facilitated by interleukin (IL)-13[3,21]. The concurrent shrinkage of zymogen granules and the upregulation of MUC granule formation are likely associated with the generation of reactive oxygen species (ROS). ROS function as inducible upstream signals in pathogenesis and are essential for normal progression. Furthermore, both acute and chronic inflammation can increase cellular ROS levels[22]. In response to oxidative stress, cells activate the CD44v9-xCT pathway[23]. Ultimately, downregulation of DNA damage induced transcript 4 (DDIT4) allows SPEM cells to reactivate mechanistic target of rapamycin (mTOR) complex 1 signaling, thereby acquiring a proliferative phenotype[24,25].

The microenvironment and alternative cellular origins

SPEM development is influenced by factors beyond epithelial cells, particularly dynamic interactions with the underlying mesenchyme (stroma). However, the specific role of the stroma in the progression of precancerous gastric lesions remains unclear. Evidence suggests that telocytes, a specialized type of mesenchymal cell, may drive metaplastic progression by secreting signaling molecules, such as Wnt and bone morphogenetic protein (BMP), thereby providing critical microenvironmental support for epithelial cells undergoing phenotypic changes[26]. The Wnt pathway is known for its key role in gastric development and regeneration, whereas BMP signaling has been implicated in the differentiation of both gastric and intestinal epithelial cells[27,28]. Furthermore, fibroblasts have been identified as the key promoters of direct carcinogenesis in SPEM cells[29].

Besides the stromal influences, the SPEM cellular origin is an area of active research. An alternative hypothesis posits that neck and progenitor cells located in the glandular isthmus also give rise to SPEM[30-32]. This suggests that chief cells are not the only cells capable of undergoing paligenosis. Notably, parietal cell precursors, which are derived from isthmus stem cells, highly express the orphan nuclear receptor gene estrogen-related receptor gamma. Deficiency in estrogen-related receptor gamma leads to impaired parietal cell differentiation, a disruption that may indirectly facilitate SPEM development[33].

ROLE OF SPEM IN GASTRIC INFLAMMATION, ATROPHY, AND DYSPLASIA

SPEM emerges in inflammatory, atrophic, and precancerous lesions as an initial response to diffuse gastric injury, representing the reprogramming of the epithelium towards a proliferative, reparative state[34]. Morphologically, SPEM is characterized by the transdifferentiation of zymogen-secreting chief cells into mucus-producing cells, which constitutes a key mucosal repair mechanism[35]. Although this response is initially adaptive, persistent inflammatory insult can lead to repeated repair cycles, thereby increasing the risk of neoplastic progression.

Inflammation is the primary trigger for this cascade, with *H. pylori* infection being the predominant risk factor. *H. pylori* activates the expression of numerous inflammatory mediators, promoting immune cell infiltration, oxidative stress, and aberrant epithelial proliferation[36]. A critical virulence factor for its survival and pathogenicity is lipopolysaccharide[37]. Lipopolysaccharide can downregulate protective cytokines, such as IL-33, impair mucosal repair[38], and induce excessive ROS accumulation, leading to DNA damage and epithelial cell death[39].

The gastric epithelium responds to such injuries through cellular plasticity, a fundamental adaptive process that balances damage and repair. Plasticity is a prerequisite for SPEM development. The nature of the epithelial response depends on the injury pattern. Localized injury often results in altered differentiation, marked by Tff2 expression and Sox9 upregulation[40], whereas diffuse injury typically triggers the full SPEM program. Notably, SPEM predominantly arises following oxyntic gland atrophy and loss of parietal cells[41]. While epithelial cells exhibit varying sensitivities to inflammatory signals, interferon-gamma (IFN- γ) has been established as a key driver that induces parietal cell atrophy, initiating the sequence of events leading to metaplasia[42,43].

Inflammation is a requisite driver for the progression of SPEM towards a more aggressive phenotype[44]. *H. pylori* can exploit this process to expand its ecological niche within the gastric mucosa[45]. Within the inflammatory milieu, the immune cells and their secreted cytokines are central to SPEM development. For instance, the activation of IL-33 and M2-type macrophages at the injury site is critical for SPEM progression[44,46,47].

At the molecular level, lineage markers upregulation, such as TFF2 and MUC6[34], along with CD44v9, helps mitigate ROS-induced oxidative stress[48]. Changes in CD44v9 expression are also linked to the downregulation of miR-148a, a potential regulator of cell fate determination[49]. Epidermal growth factor receptor (EGFR) signaling pathway role in gastric mucosal differentiation is well-established; however, the specific functions of its ligands - including transforming growth factor- α , amphiregulin, and heparin-binding epidermal growth factor-like growth factor - in SPEM remain understudied[50]. A recent study using a mouse model of acute parietal cell atrophy induced by DMP-777 demonstrated that SFN promotes mucosal repair by activating the EGFR/extracellular signal-regulated kinase pathway, thereby mediating the transdifferentiation of chief cells into SPEM cells, a process accompanied by upregulation of the AQP5 water channel[17].

When the gastric mucosa develops IM, which is characterized by the appearance of intestinal goblet cells[51], SPEM can persist in the basal layer of the incomplete IM. This subtype is associated with a high risk of gastric carcinogenesis. SPEM is widely considered a key precursor of gastric cancer. Persistent SPEM cells, under the combined pressure of a chronic inflammatory microenvironment, genetic alterations, and epigenetic dysregulation, can progressively accumulate oncogenic mutations, ultimately leading to invasive carcinoma[52,53].

In summary, SPEM is a crucial repair response to gastric mucosal injury that aims to restore epithelial integrity through cellular reprogramming. However, when driven by persistent insults such as *H. pylori* infection, glandular atrophy, and microenvironmental dysregulation, this reparative mechanism can become dysregulated. Instead of restoring homeostasis, they may initiate a pathogenic sequence that begins with metaplasia and progresses to precancerous lesions and cancer.

RELATED MODELS OF SPEM

Owing to the inherent limitations in studying the pathogenesis and interventions directly in humans, mouse models have become indispensable for investigating spasmodic SPEM and gastric precancerous progression. Their physiological relevance to humans, coupled with established genetic tools and cost-effectiveness, makes them a tractable and widely adopted system. Its key advantages include experimental controllability and phenotypic uniformity. Through genetic engineering, researchers can precisely manipulate gene expression or cell lineages *in vivo*, enabling the systematic observation of gastric mucosal changes and establishing clear causal links between molecular perturbations and histological phenotypes. Commonly utilized SPEM models fall into three categories: (1) The *H. pylori* infection-induced SPEM model, which recapitulates chronic inflammation-driven pathogenesis; (2) Acute chemical injury-induced SPEM models, which probe SPEM origins during repair and regeneration; and (3) Genetically engineered models that directly test molecular mechanisms by activating or deleting specific genes. The models used are listed in Table 1[8,54-73].

Animal models are indispensable for investigating the pathogenesis and identifying potential therapeutic targets. However, these models cannot fully recapitulate the complexity of human diseases; therefore, their findings require validation in clinical studies. For instance, *H. pylori* infection can successfully establish a mouse model of SPEM, and lesions have also been identified in humans[57]. Mouse models offer a tractable platform for the systematic study of the multistep pathogenesis. Crucially, studies in mice have demonstrated that SPEM is reversible[68]; direct evidence in humans remains limited, although eradicating *H. pylori* may halt its progression, particularly in the early stages[73]. The reversibility of IM is still debated. Therefore, advancing gastric cancer prevention requires an integrated strategy. Mouse models provide mechanistic insights and identify therapeutic candidates, as demonstrated by the signal transducer and activator of transcription 3 (STAT3) inhibitor STA-21, which limits early metaplasia[74]. These findings must then be validated in clinically relevant human models, such as patient-derived gastric organoids, to confirm their efficacy, as exemplified by luteolin reversing premalignant lesions (SPEM/IM)[75], and to accelerate clinical translation.

Table 1 Characteristics of common spasmodic polypeptide-expressing metaplasia mice

Mouse model	SPEM	SPEM for proliferation capacity	Intestinal metaplasia	Inflammatory infiltrate	Invasive glandular production	Intestinalized
<i>H. pylori</i> infection-induced SPEM models						
<i>Helicobacter felis</i> or <i>H. pylori</i> infection[54-57]	Yes	Yes	No	Yes	Yes	Yes
Acute chemical injury induced SPEM models						
DMP-777 treatment[8,54,56,58]	Yes	Yes	No	Yes	No	Yes
L635 treatment[54-56]	Yes	Yes	No	Yes	No	Yes
High-dose tamoxifen treatment[59,60]	Yes	Yes	No	Yes	No	Yes
Genetically engineered mouse models						
SOX9 overexpression mice [61]	Yes	Yes	Yes	Yes	Yes	Yes
LKB1/PTEN deficient mice [62]	Yes	Yes	Yes	Yes	Yes	Yes
Gastrin-deficient mice[63]	Yes	Yes	Yes	Yes	Yes	Yes
IL-1 β transgenic mice[64]	Yes	Yes	Yes	Yes	Yes	Yes
H/K-IFN- γ transgenic mice [65]	Yes	Yes	No	Yes	Yes	Yes
Conditional K-Ras activation mouse[66,67]	Yes	Yes	No	Yes	Yes	Yes
AR knockout mice[68]	Yes	Yes	Yes	Yes	Yes	Yes
Mist1-Kras mice[69,70]	Yes	Yes	Yes	Yes	Yes	Yes
TGF α transgenic mice (MT-TGF α or Doxi-TGF α)[71-73]	Yes	Yes	Yes	Yes	Yes	Yes

SPEM: Spasmodic polypeptide-expressing metaplasia; *H. pylori*: *Helicobacter pylori*; SOX9: SRY-Box transcription factor 9; LKB1: Liver kinase B1; PTEN: Phosphatase and tensin homolog; IL: Interleukin; IFN: Interferon; AR: Amphiregulin; Mist1: Muscle, intestine, stomach expression 1; TGF: Transforming growth factor.

EFFECT OF CYTOKINES ON THE INDUCTION OF METAPLASTIC PHENOTYPES

Cytokines play a pivotal role in shaping the tumor microenvironment, orchestrating the initiation and progression of SPEM, and significantly promoting gastric cancer development[76]. Chronic inflammation represents the initial step in diffuse gastric cancer[77] with common etiologies including autoimmune responses (accompanied by the involvement of multiple cytokines) and *H. pylori* infection, both of which lead to parietal cell atrophy and SPEM[42,78,79]. Inflammatory cytokines act as auxiliary signals following parietal cell loss and are critical for SPEM induction and progression[80]. *H. pylori* infection elicits the release of numerous cytokines, such as IL-1 β , IL-6, IL-17, IFN- γ , and tumor necrosis factor- α (TNF- α)[81]. These include pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6, IFN- γ) and anti-inflammatory cytokines (IL-10, IL-18). An imbalance between these subsets disrupts inflammatory processes, thereby contributing to metaplasia and tumorigenesis[82]. As a key component of type I immune responses, IFN- γ fosters an inflammatory milieu and serves as a major driver of SPEM development[42,43]. IL-17A, a canonical pro-inflammatory cytokine primarily secreted by T helper 17 (Th17) cells, is regulated by IL-23, a critical factor for Th17 cell differentiation and maintenance. IL-10, released by regulatory T (Treg) cells, inhibits Th17-induced inflammation; the Th17/Treg balance sustains gastric mucosal immune homeostasis while potentially promoting persistent inflammation[76,83]. *H. pylori* modulates immune escape mechanisms and polarizes dendritic cells (DCs) to secrete IL-23, which induces and maintains Th17 cells. The subsequent secretion of IL-17 and IL-21 by Th17 cells amplifies the Th17 response via IL-21-mediated positive feedback[84]. Additionally, IFN- γ and IL-17A directly induce gastric epithelial cell death, which is essential for subsequent parietal cell atrophy and SPEM progression[42,79]. TNF- α , a pro-inflammatory cytokine secreted by macrophages, activates multiple inflammation-related downstream signaling pathways and enhances gastric cancer cell metastasis[85,86]. While the precise mechanism of IL-1 β in gastric cancer remains elusive, existing data indicate that IL-1 β acts as a key mediator of inflammatory

responses, contributing to gastric precancerous lesions and suppressing gastric acid secretion, thereby facilitating gastric cancer development[81,87]. IL-6, a pleiotropic cytokine that acts primarily *via* the IL-6/STAT3 pathway, contributes to both inflammation and gastric cancer progression and promotes M2 macrophage polarization[88,89]. M2 macrophages play critical roles in gastric cancer progression and participate in angiogenesis, tumor invasion, metastasis, and therapeutic resistance[78]. DCs secrete IL-18, which acts directly on T cells to promote Treg differentiation, suppress immune responses, and facilitate persistent *H. pylori* infection[90]. IL-10, mainly secreted by macrophages and DCs, functions as an immunosuppressive cytokine that fosters an immunosuppressive microenvironment that favors the formation and progression of precancerous lesions, such as SPEM, and even creates conditions for further gastric cancer development [91].

Notably, IL-33, a member of the IL-1 family, plays a crucial role in driving SPEM as emphasized in recent studies[21,77,92,93]. IL-13 is also important for the maturation and proliferation of SPEM cells[21]. Type II immune responses have been implicated as key contributors to epithelial metaplasia, with IL-33 identified as a critical inducer and type II cytokines (IL-4 and IL-13) as major drivers[77,78]. IL-33 release and signaling trigger the upregulation of type 2 inflammatory cytokines, including IL-4 and IL-13[94]. IL-13 not only serves as a key regulator of SPEM cell generation but also promotes the maturation and proliferation of SPEM lineages[21,93]. Type 2 innate lymphoid cells play a vital role in the IL-33/IL-13 axis by initiating the release of IL-13 and IL-4, activating mast cells, and promoting M2 macrophage polarization[78] (Figure 2).

Other IL-1 family members also modulate SPEM activity. IL-36 triggers the expression of pro-inflammatory cytokines, such as IL-12, fostering a chronic inflammatory environment that perpetuates a cycle of mucosal damage and repair, thus sustaining SPEM. It can also enhance the invasive and metastatic potential of gastric cancer. Conversely, IL-38 effectively counteracts the pro-inflammatory effects of IL-36[95,96]. Given their shared family affiliations, it is plausible that IL-36 and IL-33 act synergistically to coactivate the IL-13 pathway, thereby promoting the transdifferentiation of chief cells and contributing to the initial formation of SPEM.

Besides cytokine networks, the Hippo pathway effector Yes-associated protein (YAP) is implicated in metaplastic progression. Analysis of human gastric tumor tissue revealed that nuclear YAP and HE4 expression was upregulated in metaplastic regions[97]. Both YAP and HE4 were highly expressed in SPEM and IM, suggesting that YAP activation may promote the development of these precancerous lesions, potentially through the positive regulation of SPEM-related genes such as HE4. Immune regulation also plays a counterbalancing role. In autoimmune gastritis, IL-27 has been identified as an inhibitor of CD4+ T cell-mediated inflammation in the gastric mucosa, thereby exerting a protective effect against gastritis and SPEM[46].

MicroRNAs (miRNAs) are endogenously expressed noncoding RNAs that post-transcriptionally regulate gene expression by binding to target mRNAs through sequence complementarity. They play pivotal roles in a wide array of biological processes, including cell development, differentiation, and proliferation[98-101]. The dysregulation of specific miRNAs has been implicated in gastric carcinogenesis. In SPEM, miRNAs, such as miR-21, miR-155, and miR-223, were upregulated, whereas miR-148a was downregulated. Downregulation of miR-148a may be a key event in the initiation of chief cell reprogramming[102]. During IM, lesions are influenced by other miRNAs, including miR-1, miR-30, miR-194, and miR-490[103].

A notable example is miR-30a, which is highly expressed in mucus neck cells and chief cells of normal gastric tissue in both mice and humans. However, its expression is significantly downregulated in mouse models of SPEM and IM (induced by DMP-777 or L635), including in human clinical samples of these lesions. This downregulation was observed in both GSII-positive SPEM and GSII-negative IM tissues. Reduced miR-30a levels have also been observed in human gastric cancer cells, suggesting its potential role as an early biomarker and therapeutic target to prevent gastric carcinogenesis[101,104].

Furthermore, downregulation of miR-7 has been identified as an early event in the metaplasia-carcinoma sequence. In SPEM tissues, decreased miR-7 expression was associated with the upregulation of TFF2[105]. From a therapeutic perspective, a study found that 18 β -glycyrrhetic acid suppresses proliferation, induces cell cycle arrest, and promotes apoptosis in gastric cancer cells. This compound acts by regulating the miR-328-3p/STAT3 signaling pathway and promoting autophagic flux, highlighting a potential novel pharmacological strategy for gastric cancer treatment[100].

SPEM-RELATED SIGNALING PATHWAYS

Research into the molecular mechanisms of SPEM has revealed a highly interconnected regulatory network, with key signaling pathways - including STAT3, nuclear factor kappa B (NF- κ B), mTOR, and Wnt/ β -catenin - synergistically driving the phenotypic transformation of gastric epithelial cells to promote SPEM development and maintenance (Figure 3).

Wnt signaling pathway

Wnt proteins are secreted glycoproteins whose core effector, β -catenin, plays crucial roles in cell adhesion and gene transcription[106,107]. The Wnt signaling pathway plays a pivotal role in gastric development and homeostasis. *H. pylori* infection can upregulate AQP5 *via* its virulence factor cytotoxin-associated gene A, which in turn leads to aberrant activation of the Wnt/ β -catenin pathway. This activation not only drives the progression of gastritis but also serves as a key mechanism inducing host cell dedifferentiation and SPEM formation[57,108].

During this process, ROS act as key signaling molecules. On one hand, ROS can further activate the Wnt/ β -catenin pathway to mediate hyperproliferation[109]. Conversely, chief cells can employ the peroxisome proliferator-activated

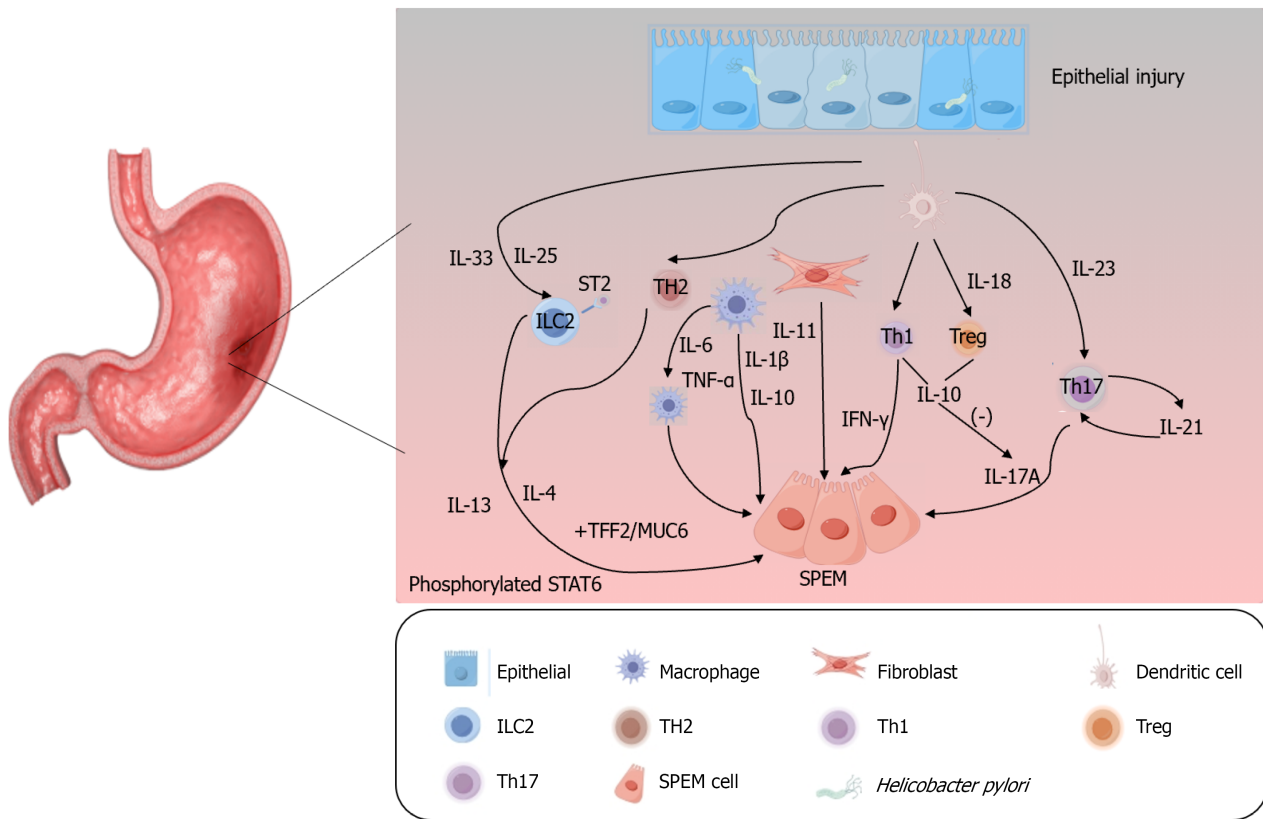


Figure 2 Cytokine-mediated induction of spasmolytic polypeptide-expressing metaplasia. *Helicobacter pylori* infection triggers a host immune response that can mimic autoimmunity, resulting in antigen-specific tissue damage. Following damage, interleukin (IL)-33 and IL-25 are released as early alarm signals, leading to the activation of various immune cells, including macrophages and T helper 1 (Th1), Th2, and Th17 cells. These activated cells secrete a combination of pro- and anti-inflammatory factors, collectively establishing a chronic inflammatory microenvironment conducive to metaplasia. Specifically, interleukin (IL)-33 (and, to a lesser extent, IL-25) binds to the ST2 receptor on type 2 innate lymphoid cells, prompting the secretion of type 2 cytokines such as IL-4 and IL-13. IL-13 and IL-4 then signal through the signal transducer and activator of transcription 6 pathway in gastric epithelial cells, promoting the expression of mucous cell markers, including trefoil factor 2 and mucin 6. This process ultimately facilitated the maturation and proliferation of spasmolytic polypeptide-expressing metaplasia cells. IL: Interleukin; ILC2s: Type 2 innate lymphoid cells; TFF2: Trefoil factor 2; MUC6: Mucin 6; STAT6: Signal transducer and activator of transcription 6; TNF: Tumor necrosis factor; IFN: Interferon; SPEM: Spasmolytic polypeptide-expressing metaplasia; TH2: T helper 2; Th1: T helper 1; Treg: Regulatory T.

receptor gamma co-activator-1 alpha-xCT-glutathione peroxidase 4 axis to regulate mitochondrial activity and manage ROS levels; a failure in ROS clearance impedes SPEM development and promotes cell death[22]. Telocytes within the microenvironment secrete signaling molecules such as Wnt5a, Bmp4, and Bmp7[26]. Substantial evidence indicates that sustained activation of the Wnt/ β -catenin pathway is closely associated with gastric cancer development, progression, and invasiveness of gastric cancer. The drug nitazoxanide effectively mitigates SPEM by inhibiting this pathway, providing an experimental basis for its potential as a therapeutic strategy[57,110].

mTOR signaling pathway

The mTOR signaling pathway is involved in the development of pathogenesis. Its activity is regulated by key factors including Ddit4 and the transcription factor Sox9, which coordinate cell cycle progression to drive cellular reprogramming[25,111]. YAP, which is specifically activated during SPEM, is a central regulator of gastric regeneration and tumorigenesis. It modulates the activity of the mTOR complex 1 via its target gene *Ddit4*, thereby promoting SPEM formation via a pathogenesis program[24,25,97].

R-spondin 3, a Wnt signaling enhancer known to regulate stem cell behavior in various organs[112,113], transiently activates YAP to promote regeneration after acute injury. However, during chronic *H. pylori* infection, sustained R-spondin 3 overexpression synergizes with signaling pathways such as mTOR and cytokines such as IL-33, driving glandular hyperplasia and the development of precancerous lesions and demonstrating long-range regulatory capabilities[114].

NF- κ B signaling pathway

The NF- κ B signaling pathway serves as a central regulator of innate and adaptive immunity and is extensively involved in controlling cell proliferation, apoptosis, migration, invasion, and inflammatory responses. It is primarily activated via the canonical pathway and plays a key role in gastric mucosal lesion development[115]. Studies have shown that deletion of the mitochondrial protein gene associated with retinoid-IFN-induced mortality 19 in parietal cells triggers SPEM formation via the ROS-NF- κ B axis. This process depends on I κ B degradation and p65 nuclear translocation, mediated by the IKK kinase complex, in which the catalytic subunit IKK α serves as a core signaling component. The resulting aberrant

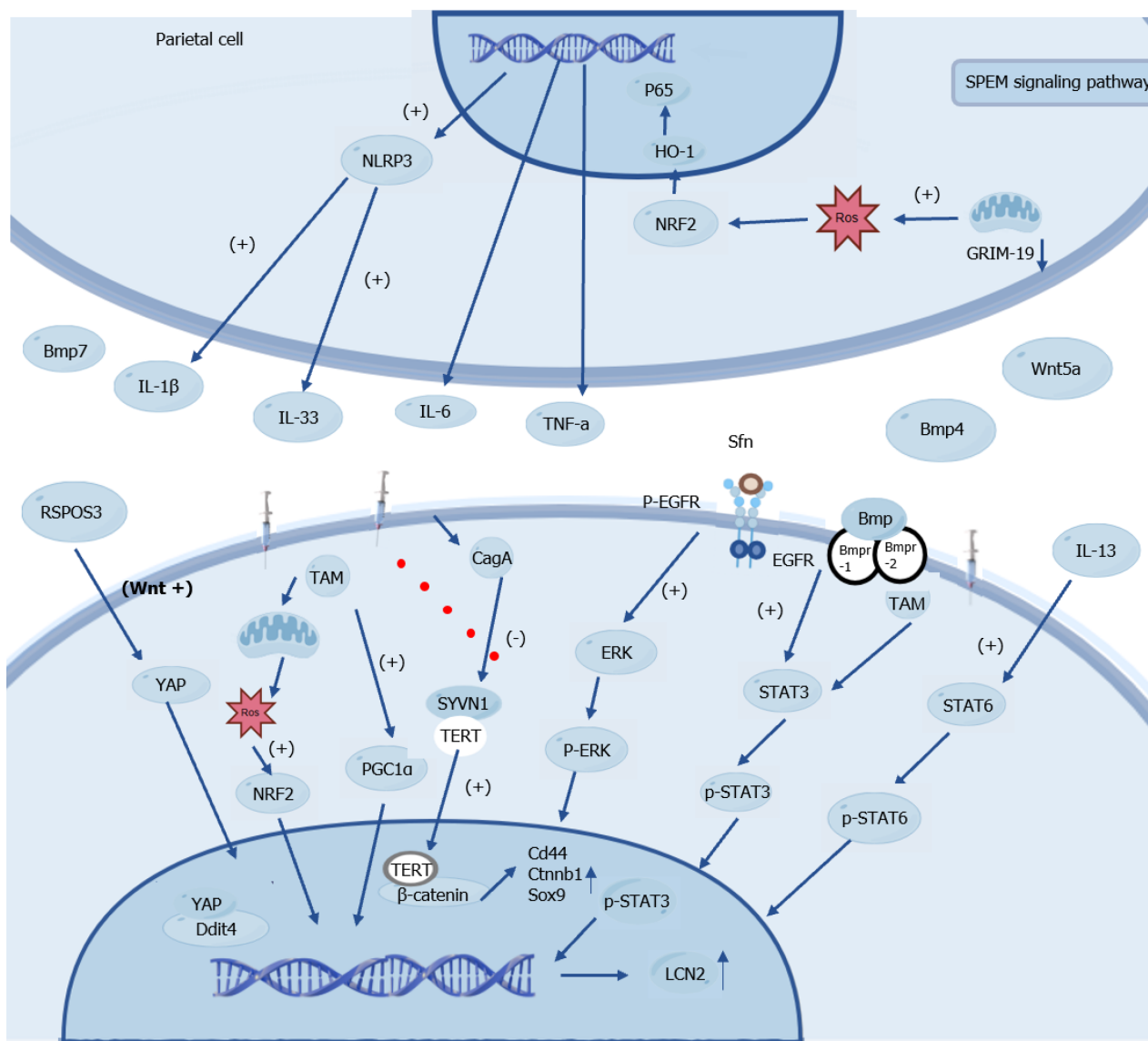


Figure 3 Interaction of key factors upstream and downstream of spasmodic polypeptide-expressing metaplasia-related signaling pathway. The figure illustrates the molecular regulatory mechanisms associated with parietal cells and the spasmodic polypeptide-expressing metaplasia signaling pathway, as evidenced in mouse models. In parietal cells, NLR family pyrin domain-containing 3 is activated by factors such as PR55, promoting the production of cytokines including interleukin (IL)-1 β , IL-33, IL-8, and tumor necrosis factor- α . Concurrently, reactive oxygen species contribute to this regulation by activating nuclear factor erythroid 2-related factor 2, which subsequently modulates downstream effectors such as heme oxygenase-1. Within the spasmodic polypeptide-expressing metaplasia signaling pathway, alterations in gene associated with retinoid-interferon-induced mortality 19 influence reactive oxygen species levels, thereby engaging in subsequent pathways, such as those involving bone morphogenetic protein. Additionally, key molecules including Yes-associated protein, telomerase reverse transcriptase, and β -catenin participate in the regulation of gene expression. For instance, lipocalin 2 expression is regulated by phosphorylated signal transducer and activator of transcription 3 within relevant signaling cascades, whereas the binding of sulforaphane to epidermal growth factor receptor activates a series of signal transduction events, such as the extracellular signal-regulated kinase pathway. Collectively, these interactions form a complex molecular regulatory network, as characterized by mouse studies. NLRP3: NLR family pyrin domain-containing 3; HO-1: Heme oxygenase-1; SPEM: Spasmodic polypeptide-expressing metaplasia; NRF2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; GRIM-19: Gene associated with retinoid-interferon-induced mortality 19; BMP: Bone morphogenetic protein; IL: Interleukin; TNF: Tumor necrosis factor; Sfn: Sulforaphane; TAM: Tamoxifen; CagA: Cytotoxin-associated gene A; EGFR: Epidermal growth factor receptor; YAP: Yes-associated protein; SYVN1: E3 ubiquitin ligase synoviolin; ERK: Extracellular signal-regulated kinase; stat3: Signal transducer and activator of transcription 3; Ddit4: DNA damage induced transcript 4; TERT: Telomerase reverse transcriptase; Sox9: SRY-Box transcription factor 9; LCN2: Lipocalin-2.

NF- κ B activation induces the release of inflammatory factors such as IL-6 and TNF- α , and cooperates with the NLR family pyrin domain-containing 3/IL-33 pathway to promote SPEM development[116,117]. Additionally, miR-130b plays a central role in driving gastric metaplasia by activating the NF- κ B pathway[118]. The Mongolian gerbil *H. pylori* infection model further confirmed that SPEM lesion formation is closely associated with sustained activation of the NF- κ B pathway [119].

STAT3 signaling pathway

STAT3 is a key transcription factor linking chronic inflammation to gastric tumorigenesis. Upon *H. pylori* infection,

cytokines, such as IL-6 and IL-11, bind to their receptors and trigger STAT3 phosphorylation at tyrosine 705. Phosphorylated STAT3 (p-STAT3) dimerizes and translocates to the nucleus, where it activates the transcription of genes involved in proliferation, apoptosis, and invasion. STAT3 signaling evolves from transient activation in early infection to sustained activation in tumors, driving the progression of gastric mucosal lesions and correlating with poor prognosis [120-122]. Concurrently, high expression levels of IL-6, p-STAT3, and Ki67 have been observed in SPEM lesions [123]. Aberrant STAT3 activation interacts with multiple regulatory mechanisms; for example, the inhibition of BMP signaling exacerbates inflammation and promotes SPEM through STAT3 upregulation [124]. In the DMP-777 mouse model, evidence suggests that SFN may engage the STAT3 pathway during the later stages of carcinogenesis [17]. Activated Ras is involved in the development of metaplasia in *Mist1-Kras* mouse principal cells [69]. IL-13 directly promotes SPEM cell proliferation and maturation *via* the STAT6 pathway [21].

Th17 cells play a significant role in autoimmune diseases, functioning in balance with Treg cells [125,126]. Tregs are lymphocytes that negatively regulate immune responses [127]. Inflammation is primarily mediated by IFN- γ -producing CD4⁺ T cells (Th1) and IL-17-producing CD4⁺ T cells (Th17) [128]. In autoimmune gastritis, STAT3 is a downstream signaling protein required for Th17 cell differentiation, and inhibition of STAT3 restores the Th17/Treg balance, thereby reducing inflammation and limiting early chemotactic changes [74]. A recent study has elucidated the immunosuppressive role of Tregs. Tregs secrete the anti-inflammatory cytokine, IL-13, which subsequently activates the STAT3 signaling pathway in gastric cancer cells through p-STAT3. This IL-13-driven p-STAT3 activation enhances the self-renewal capacity [129]. Furthermore, STAT3 acts synergistically with other oncogenic drivers. It cooperates with activated Ras to promote pathogenic sequences involved in gastric mucosal atrophy, hyperproliferation, and SPEM formation [130]. Its sustained activation can also be fueled by non-inflammatory stimuli such as the accumulation of deoxycholic acid during progression to IM [131].

Luteolin, a natural flavonoid compound widely present in various medicinal plants, has been shown to effectively block activation of the STAT3/Lipocalin 2 oncogenic signaling axis in a tamoxifen-induced mouse model in preclinical studies. Luteolin curbs the progression of metaplastic lesions *in vivo* by directly binding to STAT3 and inhibiting tyrosine phosphorylation. Luteolin curbs the progression of metaplastic lesions at the model level [75]. This demonstrates that targeted disruption of STAT3 signaling is a viable strategy for intercepting the metaplasia-carcinoma sequence.

Clinical translation strategies for SPEM

The complex, intricate molecular network governing SPEM unveils a strategic roadmap for clinical intervention. Moving beyond a one-size-fits-all approach, we propose a precision defense framework aimed at intercepting the metaplasia-carcinoma sequence at its most vulnerable points. Based on the current understanding of SPEM's multi-pathway regulatory networks, a stratified interventional framework has emerged. For early detection, the integrated assessment of TFF2/MUC6/CD44v9 protein expression profiles with characteristic miRNA signatures (miR-148a/miR-30a/miR-21) in the gastric mucosa or body fluids enables precise risk stratification of premalignant lesions. Therapeutically, beyond fundamental *H. pylori* eradication [55], targeting key pathway nodes shows promise as inhibitors of the IL-33/IL-13 axis and STAT3 signaling hub (*e.g.*, luteolin), along with EGFR/extracellular signal-regulated kinase pathway agonists (*e.g.*, SFN), providing targeted chemoprevention against the inflammation-metaplasia cascade. Additional potential targets include the Wnt/ β -catenin pathway (modulated by nitazoxanide in preclinical studies), mTOR signaling, and the YAP-DDIT4 axis in cellular dedifferentiation. Implementation requires biomarker-guided patient stratification using markers such as CD44 and p-STAT3. Synthetic lethality strategies that leverage ROS metabolic characteristics and combination therapies represent promising research directions for establishing a comprehensive SPEM management system.

CONCLUSION

Based on the synthesis of recent advances regarding the cellular origins of SPEM and its key signaling pathways - such as NF- κ B, YAP, STAT3, and Wnt/ β -catenin - it must be noted that current investigations into these pathways remain incomplete, with a limited number of experimental studies. Nevertheless, these pathways collectively regulate the initiation and progression of SPEM, underscoring the need to prioritize signaling pathway research in future investigative strategies. Accumulating evidence has demonstrated that SPEM is not merely an adaptive repair response of the gastric mucosa to injury, but more importantly, a precancerous lesion that actively promotes gastric carcinogenesis. As a dynamic biological process at the crossroads of regeneration and cancer, SPEM represents a crucial target for early-stage targetable interventions. Therefore, deepening our understanding of SPEM mechanisms is essential for the early detection and prevention of gastric cancer.

ACKNOWLEDGEMENTS

I would like to sincerely thank my supervisor, Professor Tai-Peng Tan, for his invaluable guidance, unwavering support, and profound intellectual inspiration throughout this research. His expertise in cancer research and rigorous academic insights were instrumental in shaping this work. I am also grateful for his patience and encouragement, which have greatly facilitated my academic growth. This study would not have been possible without his generous mentorship.

FOOTNOTES

Author contributions: Yang RR and Yan YR contributed equally to this study as co-first authors. Yang RR and Yan YR contributed to the conceptualization of the study, interpretation of the data, and wrote the manuscript; Li YF revised the manuscript.

Supported by Liaoning Provincial Science and Technology Plan Joint Plan (Applied Basic Research Program), No. 2023JH2/101700226; and Liaoning Provincial Traditional Chinese Medicine Interdisciplinary Innovation Team Project, No. LNZYXCXTD-JCCX-002.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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

Country of origin: China

ORCID number: Yu-Feng Li 0009-0005-3860-8411.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Xu ZH

REFERENCES

- 1 **Bray F**, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024; **74**: 229-263 [RCA] [PMID: 38572751 DOI: 10.3322/caac.21834] [FullText]
- 2 **Li W**, Zhang T. Precancerous pathways to gastric cancer: a review of experimental animal models recapitulating the Correa cascade. *Front Cell Dev Biol* 2025; **13**: 1620756 [RCA] [PMID: 40673273 DOI: 10.3389/fcell.2025.1620756] [FullText] [Full Text(PDF)]
- 3 **Goldenring JR**, Mills JC. Cellular Plasticity, Reprogramming, and Regeneration: Metaplasia in the Stomach and Beyond. *Gastroenterology* 2022; **162**: 415-430 [RCA] [PMID: 34728185 DOI: 10.1053/j.gastro.2021.10.036] [FullText]
- 4 **Goldenring JR**, Nam KT, Wang TC, Mills JC, Wright NA. Spasmolytic polypeptide-expressing metaplasia and intestinal metaplasia: time for reevaluation of metaplasias and the origins of gastric cancer. *Gastroenterology* 2010; **138**: 2207-2210, 2210.e1 [RCA] [PMID: 20450866 DOI: 10.1053/j.gastro.2010.04.023] [FullText] [Full Text(PDF)]
- 5 **Deng Z**, Zhu J, Ma Z, Yi Z, Tuo B, Li T, Liu X. The mechanisms of gastric mucosal injury: focus on initial chief cell loss as a key target. *Cell Death Discov* 2023; **9**: 29 [RCA] [PMID: 36693845 DOI: 10.1038/s41420-023-01318-z] [FullText]
- 6 **Burclaff J**, Osaki LH, Liu D, Goldenring JR, Mills JC. Targeted Apoptosis of Parietal Cells Is Insufficient to Induce Metaplasia in Stomach. *Gastroenterology* 2017; **152**: 762-766.e7 [RCA] [PMID: 27932312 DOI: 10.1053/j.gastro.2016.12.001] [FullText]
- 7 **Schmidt PH**, Lee JR, Joshi V, Playford RJ, Poulosom R, Wright NA, Goldenring JR. Identification of a metaplastic cell lineage associated with human gastric adenocarcinoma. *Lab Invest* 1999; **79**: 639-646 [RCA] [PMID: 10378506] [FullText] [Full Text(PDF)]
- 8 **Nomura S**, Yamaguchi H, Ogawa M, Wang TC, Lee JR, Goldenring JR. Alterations in gastric mucosal lineages induced by acute oxyntic atrophy in wild-type and gastrin-deficient mice. *Am J Physiol Gastrointest Liver Physiol* 2005; **288**: G362-G375 [RCA] [PMID: 15647607 DOI: 10.1152/ajpgi.00160.2004] [FullText]
- 9 **Hoffmann W**. TFF2, a MUC6-binding lectin stabilizing the gastric mucus barrier and more (Review). *Int J Oncol* 2015; **47**: 806-816 [RCA] [PMID: 26201258 DOI: 10.3892/ijo.2015.3090] [FullText]
- 10 **Jencks DS**, Adam JD, Borum ML, Koh JM, Stephen S, Doman DB. Overview of Current Concepts in Gastric Intestinal Metaplasia and Gastric Cancer. *Gastroenterol Hepatol (N Y)* 2018; **14**: 92-101 [RCA] [PMID: 29606921] [FullText]
- 11 **Can N**, Oz Puyan F, Altaner S, Ozyilmaz F, Tokuc B, Pehlivanoglu Z, Kutlu KA. Mucins, trefoil factors and pancreatic duodenal homeobox 1 expression in spasmolytic polypeptide expressing metaplasia and intestinal metaplasia adjacent to gastric carcinomas. *Arch Med Sci* 2020; **16**: 1402-1410 [RCA] [PMID: 33224340 DOI: 10.5114/aoms.2013.36923] [FullText] [Full Text(PDF)]
- 12 **Burclaff J**, Willet SG, Sáenz JB, Mills JC. Proliferation and Differentiation of Gastric Mucous Neck and Chief Cells During Homeostasis and Injury-induced Metaplasia. *Gastroenterology* 2020; **158**: 598-609.e5 [RCA] [PMID: 31589873 DOI: 10.1053/j.gastro.2019.09.037] [FullText]
- 13 **Brown JW**, Cho CJ, Mills JC. Paligenosis: Cellular Remodeling During Tissue Repair. *Annu Rev Physiol* 2022; **84**: 461-483 [RCA] [PMID: 34705482 DOI: 10.1146/annurev-physiol-061121-035954] [FullText]
- 14 **Lennerz JK**, Kim SH, Oates EL, Huh WJ, Doherty JM, Tian X, Bredemeyer AJ, Goldenring JR, Lauwers GY, Shin YK, Mills JC. The transcription factor MIST1 is a novel human gastric chief cell marker whose expression is lost in metaplasia, dysplasia, and carcinoma. *Am J Pathol* 2010; **177**: 1514-1533 [RCA] [PMID: 20709804 DOI: 10.2353/ajpath.2010.100328] [FullText] [Full Text(PDF)]
- 15 **Brown JW**, Lin X, Nicolazzi GA, Liu X, Nguyen T, Radyk MD, Burclaff J, Mills JC. Cathartocytosis: Jettisoning of cellular material during reprogramming of differentiated cells. *Cell Rep* 2025; **44**: 116070 [RCA] [PMID: 40742812 DOI: 10.1016/j.celrep.2025.116070] [FullText] [Full Text(PDF)]
- 16 **Radyk MD**, Spatz LB, Peña BL, Brown JW, Burclaff J, Cho CJ, Kefaloy Y, Shih CC, Fitzpatrick JA, Mills JC. ATF3 induces RAB7 to govern autodegradation in paligenosis, a conserved cell plasticity program. *EMBO Rep* 2021; **22**: e51806 [RCA] [PMID: 34309175 DOI: 10.15252/embr.202051806] [FullText]
- 17 **Won Y**, Sohn Y, Lee SH, Goldstein A, Gangula R, Mallal S, Goldenring JR. Stratifin Is Necessary for Spasmolytic Polypeptide-Expressing Metaplasia Development After Acute Gastric Injury. *Cell Mol Gastroenterol Hepatol* 2025; **19**: 101521 [RCA] [PMID: 40280276 DOI: 10.1016/j.cmhgh.2025.101521] [FullText]

- 10.1016/j.jcmgh.2025.101521] [FullText] [Full Text(PDF)]
- 18 Lee SH, Jang B, Min J, Contreras-Panta EW, Presentation KS, Delgado AG, Piazuolo MB, Choi E, Goldenring JR. Up-regulation of Aquaporin 5 Defines Spasmodic Polypeptide-Expressing Metaplasia and Progression to Incomplete Intestinal Metaplasia. *Cell Mol Gastroenterol Hepatol* 2022; **13**: 199-217 [RCA] [PMID: 34455107 DOI: 10.1016/j.jcmgh.2021.08.017] [FullText] [Full Text(PDF)]
- 19 Willet SG, Thanintorn N, McNeill H, Huh SH, Ormitz DM, Huh WJ, Hoft SG, DiPaolo RJ, Mills JC. SOX9 Governs Gastric Mucous Neck Cell Identity and Is Required for Injury-Induced Metaplasia. *Cell Mol Gastroenterol Hepatol* 2023; **16**: 325-339 [RCA] [PMID: 37270061 DOI: 10.1016/j.jcmgh.2023.05.009] [FullText] [Full Text(PDF)]
- 20 Souza RF, Spechler SJ. Mechanisms and pathophysiology of Barrett oesophagus. *Nat Rev Gastroenterol Hepatol* 2022; **19**: 605-620 [RCA] [PMID: 35672395 DOI: 10.1038/s41575-022-00622-w] [FullText]
- 21 Contreras-Panta EW, Lee SH, Won Y, Norlander AE, Simmons AJ, Peebles RS Jr, Lau KS, Choi E, Goldenring JR. Interleukin 13 Promotes Maturation and Proliferation in Metaplastic Gastroids. *Cell Mol Gastroenterol Hepatol* 2024; **18**: 101366 [RCA] [PMID: 38815928 DOI: 10.1016/j.jcmgh.2024.101366] [FullText] [Full Text(PDF)]
- 22 Miao ZF, Sun JX, Huang XZ, Bai S, Pang MJ, Li JY, Chen HY, Tong QY, Ye SY, Wang XY, Hu XH, Li JY, Zou JW, Xu W, Yang JH, Lu X, Mills JC, Wang ZN. Metaplastic regeneration in the mouse stomach requires a reactive oxygen species pathway. *Dev Cell* 2024; **59**: 1175-1191.e7 [RCA] [PMID: 38521055 DOI: 10.1016/j.devcel.2024.03.002] [FullText]
- 23 Meyer AR, Engevik AC, Willet SG, Williams JA, Zou Y, Massion PP, Mills JC, Choi E, Goldenring JR. Cystine/Glutamate Antiporter (xCT) Is Required for Chief Cell Plasticity After Gastric Injury. *Cell Mol Gastroenterol Hepatol* 2019; **8**: 379-405 [RCA] [PMID: 31071489 DOI: 10.1016/j.jcmgh.2019.04.015] [FullText] [Full Text(PDF)]
- 24 Miao ZF, Sun JX, Adkins-Threats M, Pang MJ, Zhao JH, Wang X, Tang KW, Wang ZN, Mills JC. DDIT4 Licenses Only Healthy Cells to Proliferate During Injury-induced Metaplasia. *Gastroenterology* 2021; **160**: 260-271.e10 [RCA] [PMID: 32956680 DOI: 10.1053/j.gastro.2020.09.016] [FullText]
- 25 Miao ZF, Cho CJ, Wang ZN, Mills JC. Autophagy repurposes cells during paligenesis. *Autophagy* 2021; **17**: 588-589 [RCA] [PMID: 33280496 DOI: 10.1080/15548627.2020.1857080] [FullText]
- 26 Sohn Y, Flores Semyonov B, El-Mekkoussi H, Wright CVE, Kaestner KH, Choi E, Goldenring JR. Telocyte Recruitment During the Emergence of a Metaplastic Niche in the Stomach. *Cell Mol Gastroenterol Hepatol* 2024; **18**: 101347 [RCA] [PMID: 38670488 DOI: 10.1016/j.jcmgh.2024.04.004] [FullText]
- 27 Maloum F, Allaire JM, Gagné-Sansfaçon J, Roy E, Belleville K, Sarret P, Morisset J, Carrier JC, Mishina Y, Kaestner KH, Perreault N. Epithelial BMP signaling is required for proper specification of epithelial cell lineages and gastric endocrine cells. *Am J Physiol Gastrointest Liver Physiol* 2011; **300**: G1065-G1079 [RCA] [PMID: 21415412 DOI: 10.1152/ajpgi.00176.2010] [FullText]
- 28 Auclair BA, Benoit YD, Rivard N, Mishina Y, Perreault N. Bone morphogenetic protein signaling is essential for terminal differentiation of the intestinal secretory cell lineage. *Gastroenterology* 2007; **133**: 887-896 [RCA] [PMID: 17678919 DOI: 10.1053/j.gastro.2007.06.066] [Full Text]
- 29 Lee SH, Contreras Panta EW, Gibbs D, Won Y, Min J, Zhang C, Roland JT, Hong SH, Sohn Y, Krystofiak E, Jang B, Ferri L, Sangwan V, Ragoussis J, Camilleri-Broët S, Caruso J, Chen-Tanyolac C, Strasser M, Gascard P, Tlsty TD, Huang S, Choi E, Goldenring JR. Apposition of Fibroblasts With Metaplastic Gastric Cells Promotes Dysplastic Transition. *Gastroenterology* 2023; **165**: 374-390 [RCA] [PMID: 37196797 DOI: 10.1053/j.gastro.2023.04.038] [FullText] [Full Text(PDF)]
- 30 Hayakawa Y, Fox JG, Wang TC. The Origins of Gastric Cancer From Gastric Stem Cells: Lessons From Mouse Models. *Cell Mol Gastroenterol Hepatol* 2017; **3**: 331-338 [RCA] [PMID: 28462375 DOI: 10.1016/j.jcmgh.2017.01.013] [FullText] [Full Text(PDF)]
- 31 Hayakawa Y, Wang TC. Isthmus Progenitors, Not Chief Cells, Are the Likely Origin of Metaplasia in eR1-CreERT; LSL-Kras(G12D) Mice. *Gastroenterology* 2017; **152**: 2078-2079 [RCA] [PMID: 28478152 DOI: 10.1053/j.gastro.2017.02.043] [FullText]
- 32 Hata M, Kinoshita H, Hayakawa Y, Konishi M, Tsuboi M, Oya Y, Kurokawa K, Hayata Y, Nakagawa H, Tateishi K, Fujiwara H, Hirata Y, Worthley DL, Muranishi Y, Furukawa T, Kon S, Tomita H, Wang TC, Koike K. GPR30-Expressing Gastric Chief Cells Do Not Dedifferentiate But Are Eliminated via PDK-Dependent Cell Competition During Development of Metaplasia. *Gastroenterology* 2020; **158**: 1650-1666.e15 [RCA] [PMID: 32032583 DOI: 10.1053/j.gastro.2020.01.046] [FullText]
- 33 Adkins-Threats M, Arimura S, Huang YZ, Divenko M, To S, Mao H, Zeng Y, Hwang JY, Burclaff JR, Jain S, Mills JC. Metabolic regulator ERRγ governs gastric stem cell differentiation into acid-secreting parietal cells. *Cell Stem Cell* 2024; **31**: 886-903.e8 [RCA] [PMID: 38733994 DOI: 10.1016/j.stem.2024.04.016] [FullText]
- 34 Engevik AC, Feng R, Choi E, White S, Bertaux-Skeirik N, Li J, Mahe MM, Aihara E, Yang L, DiPasquale B, Oh S, Engevik KA, Giraud AS, Montrose MH, Medvedovic M, Helmrath MA, Goldenring JR, Zavros Y. The Development of Spasmodic Polypeptide/TFF2-Expressing Metaplasia (SPEM) During Gastric Repair Is Absent in the Aged Stomach. *Cell Mol Gastroenterol Hepatol* 2016; **2**: 605-624 [RCA] [PMID: 27990460 DOI: 10.1016/j.jcmgh.2016.05.004] [FullText] [Full Text(PDF)]
- 35 Meyer AR, Goldenring JR. Injury, repair, inflammation and metaplasia in the stomach. *J Physiol* 2018; **596**: 3861-3867 [RCA] [PMID: 29427515 DOI: 10.1113/JP275512] [FullText]
- 36 Garabatos N, Angelats E, Santamaria P. Mechanistic and therapeutic advances in immune-mediated gastrointestinal disorders. *J Allergy Clin Immunol* 2025; **156**: 1133-1159 [RCA] [PMID: 40783002 DOI: 10.1016/j.jaci.2025.07.024] [FullText]
- 37 Chey WD, Howden CW, Moss SF, Morgan DR, Greer KB, Grover S, Shah SC. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. *Am J Gastroenterol* 2024; **119**: 1730-1753 [RCA] [PMID: 39626064 DOI: 10.14309/ajg.0000000000002968] [FullText]
- 38 Gonciarz W, Krupa A, Moran AP, Tomaszewska A, Chmiela M. Interference of LPS H. pylori with IL-33-Driven Regeneration of Caviae porcellus Primary Gastric Epithelial Cells and Fibroblasts. *Cells* 2021; **10**: 1385 [RCA] [PMID: 34199843 DOI: 10.3390/cells10061385] [Full Text] [Full Text(PDF)]
- 39 Sah DK, Arjunan A, Lee B, Jung YD. Reactive Oxygen Species and H. pylori Infection: A Comprehensive Review of Their Roles in Gastric Cancer Development. *Antioxidants (Basel)* 2023; **12**: 1712 [RCA] [PMID: 37760015 DOI: 10.3390/antiox12091712] [FullText]
- 40 Aihara E, Matthis AL, Karns RA, Engevik KA, Jiang P, Wang J, Yacyshyn BR, Montrose MH. Epithelial Regeneration After Gastric Ulceration Causes Prolonged Cell-Type Alterations. *Cell Mol Gastroenterol Hepatol* 2016; **2**: 625-647 [RCA] [PMID: 27766298 DOI: 10.1016/j.jcmgh.2016.05.005] [FullText] [Full Text(PDF)]
- 41 Goldenring JR, Nomura S. Differentiation of the gastric mucosa III. Animal models of oxyntic atrophy and metaplasia. *Am J Physiol Gastrointest Liver Physiol* 2006; **291**: G999-1004 [RCA] [PMID: 17090722 DOI: 10.1152/ajpgi.00187.2006] [FullText]
- 42 Osaki LH, Bockerstett KA, Wong CF, Ford EL, Madison BB, DiPaolo RJ, Mills JC. Interferon-γ directly induces gastric epithelial cell death

- and is required for progression to metaplasia. *J Pathol* 2019; **247**: 513-523 [RCA] [PMID: 30511397 DOI: 10.1002/path.5214] [FullText]
- 43 **Bockerstett KA**, DiPaolo RJ. Regulation of Gastric Carcinogenesis by Inflammatory Cytokines. *Cell Mol Gastroenterol Hepatol* 2017; **4**: 47-53 [RCA] [PMID: 28560288 DOI: 10.1016/j.jcmgh.2017.03.005] [FullText] [Full Text(PDF)]
- 44 **Petersen CP**, Weis VG, Nam KT, Sousa JF, Fingleton B, Goldenring JR. Macrophages promote progression of spasmodic polypeptide-expressing metaplasia after acute loss of parietal cells. *Gastroenterology* 2014; **146**: 1727-38.e8 [RCA] [PMID: 24534633 DOI: 10.1053/j.gastro.2014.02.007] [FullText]
- 45 **Sáenz JB**, Vargas N, Mills JC. Tropism for Spasmodic Polypeptide-Expressing Metaplasia Allows *Helicobacter pylori* to Expand Its Intra-gastric Niche. *Gastroenterology* 2019; **156**: 160-174.e7 [RCA] [PMID: 30287170 DOI: 10.1053/j.gastro.2018.09.050] [FullText]
- 46 **Bockerstett KA**, Petersen CP, Noto CN, Kuehm LM, Wong CF, Ford EL, Teague RM, Mills JC, Goldenring JR, DiPaolo RJ. Interleukin 27 Protects From Gastric Atrophy and Metaplasia During Chronic Autoimmune Gastritis. *Cell Mol Gastroenterol Hepatol* 2020; **10**: 561-579 [RCA] [PMID: 32376420 DOI: 10.1016/j.jcmgh.2020.04.014] [FullText] [Full Text(PDF)]
- 47 **Ding L**, Chakrabarti J, Sheriff S, Li Q, Thi Hong HN, Sontz RA, Mendoza ZE, Schreiber A, Helmrath MA, Zavros Y, Merchant JL. Toll-like Receptor 9 Pathway Mediates Schlafen(+)-MDSC Polarization During *Helicobacter*-induced Gastric Metaplasias. *Gastroenterology* 2022; **163**: 411-425.e4 [RCA] [PMID: 35487288 DOI: 10.1053/j.gastro.2022.04.031] [FullText] [Full Text(PDF)]
- 48 **Wada T**, Ishimoto T, Seishima R, Tsuchihashi K, Yoshikawa M, Oshima H, Oshima M, Masuko T, Wright NA, Furuhashi S, Hirashima K, Baba H, Kitagawa Y, Saya H, Nagano O. Functional role of CD44v-xCT system in the development of spasmodic polypeptide-expressing metaplasia. *Cancer Sci* 2013; **104**: 1323-1329 [RCA] [PMID: 23848514 DOI: 10.1111/cas.12236] [FullText]
- 49 **Shimizu T**, Sohn Y, Choi E, Petersen CP, Prasad N, Goldenring JR. Decrease in MiR-148a Expression During Initiation of Chief Cell Transdifferentiation. *Cell Mol Gastroenterol Hepatol* 2020; **9**: 61-78 [RCA] [PMID: 31473306 DOI: 10.1016/j.jcmgh.2019.08.008] [FullText] [Full Text(PDF)]
- 50 **Nam KT**, Varro A, Coffey RJ, Goldenring JR. Potentiation of oxyntic atrophy-induced gastric metaplasia in amphiregulin-deficient mice. *Gastroenterology* 2007; **132**: 1804-1819 [RCA] [PMID: 17484876 DOI: 10.1053/j.gastro.2007.03.040] [FullText]
- 51 **Correa P**. A human model of gastric carcinogenesis. *Cancer Res* 1988; **48**: 3554-3560 [RCA] [PMID: 3288329] [FullText]
- 52 **Goldenring JR**. Spasmodic polypeptide-expressing metaplasia (SPEM) cell lineages can be an origin of gastric cancer. *J Pathol* 2023; **260**: 109-111 [RCA] [PMID: 37145865 DOI: 10.1002/path.6089] [FullText]
- 53 **Kumagai K**, Shimizu T, Nikaido M, Hirano T, Kakiuchi N, Takeuchi Y, Minamiguchi S, Sakurai T, Teramura M, Utsumi T, Hiramatsu Y, Nakanishi Y, Takai A, Miyamoto S, Ogawa S, Seno H. On the origin of gastric tumours: analysis of a case with intramucosal gastric carcinoma and oxyntic gland adenoma. *J Pathol* 2023; **259**: 362-368 [RCA] [PMID: 36625379 DOI: 10.1002/path.6050] [FullText]
- 54 **Nam KT**, Lee HJ, Sousa JF, Weis VG, O'Neal RL, Finke PE, Romero-Gallo J, Shi G, Mills JC, Peek RM Jr, Konieczny SF, Goldenring JR. Mature chief cells are cryptic progenitors for metaplasia in the stomach. *Gastroenterology* 2010; **139**: 2028-2037.e9 [RCA] [PMID: 20854822 DOI: 10.1053/j.gastro.2010.09.005] [FullText] [Full Text(PDF)]
- 55 **Yoshizawa N**, Takenaka Y, Yamaguchi H, Tetsuya T, Tanaka H, Tatematsu M, Nomura S, Goldenring JR, Kaminishi M. Emergence of spasmodic polypeptide-expressing metaplasia in Mongolian gerbils infected with *Helicobacter pylori*. *Lab Invest* 2007; **87**: 1265-1276 [RCA] [PMID: 18004396 DOI: 10.1038/labinvest.3700682] [FullText]
- 56 **Weis VG**, Sousa JF, LaFleur BJ, Nam KT, Weis JA, Finke PE, Ameen NA, Fox JG, Goldenring JR. Heterogeneity in mouse spasmodic polypeptide-expressing metaplasia lineages identifies markers of metaplastic progression. *Gut* 2013; **62**: 1270-1279 [RCA] [PMID: 22773549 DOI: 10.1136/gutjnl-2012-302401] [FullText]
- 57 **He L**, Zhang X, Zhang S, Wang Y, Hu W, Li J, Liu Y, Liao Y, Peng X, Li J, Zhao H, Wang L, Lv YF, Hu CJ, Yang SM. H. Pylori-Facilitated TERT/Wnt/ β -Catenin Triggers Spasmodic Polypeptide-Expressing Metaplasia and Oxyntic Atrophy. *Adv Sci (Weinh)* 2025; **12**: e2401227 [RCA] [PMID: 39587848 DOI: 10.1002/advs.202401227] [FullText]
- 58 **Goldenring JR**, Ray GS, Coffey RJ, Meunier PC, Haley PJ, Barnes TB, Car BD. Reversible drug-induced oxyntic atrophy in rats. *Gastroenterology* 2000; **118**: 1080-1093 [RCA] [PMID: 10833483 DOI: 10.1016/s0016-5085(00)70361-1] [FullText]
- 59 **Huh WJ**, Khurana SS, Geahlen JH, Kohli K, Waller RA, Mills JC. Tamoxifen induces rapid, reversible atrophy, and metaplasia in mouse stomach. *Gastroenterology* 2012; **142**: 21-24.e7 [RCA] [PMID: 22001866 DOI: 10.1053/j.gastro.2011.09.050] [FullText]
- 60 **Saenz JB**, Burclaff J, Mills JC. Modeling Murine Gastric Metaplasia Through Tamoxifen-Induced Acute Parietal Cell Loss. *Methods Mol Biol* 2016; **1422**: 329-339 [RCA] [PMID: 27246044 DOI: 10.1007/978-1-4939-3603-8_28] [FullText]
- 61 **Chen Q**, Weng K, Lin M, Jiang M, Fang Y, Chung SSW, Huang X, Zhong Q, Liu Z, Huang Z, Lin J, Li P, El-Rifai W, Zaika A, Li H, Rustgi AK, Nakagawa H, Abrams JA, Wang TC, Lu C, Huang C, Que J. SOX9 Modulates the Transformation of Gastric Stem Cells Through Biased Symmetric Cell Division. *Gastroenterology* 2023; **164**: 1119-1136.e12 [RCA] [PMID: 36740200 DOI: 10.1053/j.gastro.2023.01.037] [Full Text]
- 62 **Fang KT**, Hung H, Lau NYS, Chi JH, Wu DC, Cheng KH. Development of a Genetically Engineered Mouse Model Recapitulating LKB1 and PTEN Deficiency in Gastric Cancer Pathogenesis. *Cancers (Basel)* 2023; **15**: 5893 [RCA] [PMID: 38136437 DOI: 10.3390/cancers15245893] [FullText]
- 63 **Zavros Y**, Eaton KA, Kang W, Rathinavelu S, Katukuri V, Kao JY, Samuelson LC, Merchant JL. Chronic gastritis in the hypochlorhydric gastrin-deficient mouse progresses to adenocarcinoma. *Oncogene* 2005; **24**: 2354-2366 [RCA] [PMID: 15735748 DOI: 10.1038/sj.onc.1208407] [FullText]
- 64 **Tu S**, Bhagat G, Cui G, Takaishi S, Kurt-Jones EA, Rickman B, Betz KS, Penz-Oesterreicher M, Bjorkdahl O, Fox JG, Wang TC. Overexpression of interleukin-1beta induces gastric inflammation and cancer and mobilizes myeloid-derived suppressor cells in mice. *Cancer Cell* 2008; **14**: 408-419 [RCA] [PMID: 18977329 DOI: 10.1016/j.ccr.2008.10.011] [FullText] [Full Text(PDF)]
- 65 **Syu LJ**, El-Zaatari M, Eaton KA, Liu Z, Tatarbe M, Keeley TM, Pero J, Ferris J, Wilbert D, Kaatz A, Zheng X, Qiao X, Grachtchouk M, Gumucio DL, Merchant JL, Samuelson LC, Dlugosz AA. Transgenic expression of interferon- γ in mouse stomach leads to inflammation, metaplasia, and dysplasia. *Am J Pathol* 2012; **181**: 2114-2125 [RCA] [PMID: 23036899 DOI: 10.1016/j.ajpath.2012.08.017] [FullText]
- 66 **Matkar SS**, Durham A, Brice A, Wang TC, Rustgi AK, Hua X. Systemic activation of K-ras rapidly induces gastric hyperplasia and metaplasia in mice. *Am J Cancer Res* 2011; **1**: 432-445 [RCA] [PMID: 21761008] [FullText] [Full Text(PDF)]
- 67 **Chung WC**, Zhou Y, Atfi A, Xu K. Downregulation of Notch Signaling in Kras-Induced Gastric Metaplasia. *Neoplasia* 2019; **21**: 810-821 [RCA] [PMID: 31276933 DOI: 10.1016/j.neo.2019.06.003] [FullText] [Full Text(PDF)]
- 68 **Nam KT**, Lee HJ, Mok H, Romero-Gallo J, Crowe JE Jr, Peek RM Jr, Goldenring JR. Amphiregulin-deficient mice develop spasmodic polypeptide expressing metaplasia and intestinal metaplasia. *Gastroenterology* 2009; **136**: 1288-1296 [RCA] [PMID: 19230855 DOI: 10.1053/j.gastro.2009.06.003] [FullText]

- 10.1053/j.gastro.2008.12.037] [FullText] [Full Text(PDF)]
- 69 **Choi E**, Hendley AM, Bailey JM, Leach SD, Goldenring JR. Expression of Activated Ras in Gastric Chief Cells of Mice Leads to the Full Spectrum of Metaplastic Lineage Transitions. *Gastroenterology* 2016; **150**: 918-30.e13 [RCA] [PMID: 26677984 DOI: 10.1053/j.gastro.2015.11.049] [FullText]
- 70 **Jang B**, Kim H, Lee SH, Won Y, Kaji I, Coffey RJ, Choi E, Goldenring JR. Dynamic tuft cell expansion during gastric metaplasia and dysplasia. *J Pathol Clin Res* 2024; **10**: e352 [RCA] [PMID: 38117182 DOI: 10.1002/cjp.2.352] [FullText] [Full Text(PDF)]
- 71 **Gabriel TT**, Park JD, Madala SK, Coffey RJ, Huh WJ. Development of Mouse Models for Ménétrier's Disease. *J Vis Exp* 2025 [RCA] [PMID: 40549725 DOI: 10.3791/67981] [FullText] [Full Text(PDF)]
- 72 **Garcia-Carracedo D**, Yu CC, Akhavan N, Fine SA, Schönleben F, Maehara N, Karg DC, Xie C, Qiu W, Fine RL, Remotti HE, Su GH. Smad4 loss synergizes with TGF α overexpression in promoting pancreatic metaplasia, PanIN development, and fibrosis. *PLoS One* 2015; **10**: e0120851 [RCA] [PMID: 25803032 DOI: 10.1371/journal.pone.0120851] [FullText] [Full Text(PDF)]
- 73 **Nomura S**, Settle SH, Leys CM, Means AL, Peek RM Jr, Leach SD, Wright CV, Coffey RJ, Goldenring JR. Evidence for repatterning of the gastric fundic epithelium associated with Ménétrier's disease and TGF α overexpression. *Gastroenterology* 2005; **128**: 1292-1305 [RCA] [PMID: 15887112 DOI: 10.1053/j.gastro.2005.03.019] [FullText]
- 74 **Zhang A**, Niu L, Ni Y, Liu W, Gao X, Chang L, Cao P. STAT3 inhibition mitigates experimental autoimmune gastritis by restoring Th17/Treg immune balance. *Immunol Res* 2025; **73**: 90 [RCA] [PMID: 40471463 DOI: 10.1007/s12026-025-09643-4] [FullText]
- 75 **Hao X**, Yuan S, Ning J, Zhou Y, Lang Y, Han X, Meng Q, Xiong Y, Cui R, Gong Y, Ma C, Xu W, Wang Y, Guo X, Wang C, Zhang J, Fu W, Ding S. Luteolin improves precancerous conditions of the gastric mucosa by binding STAT3 and inhibiting LCN2 expression. *Int J Biol Sci* 2025; **21**: 3397-3415 [RCA] [PMID: 40520011 DOI: 10.7150/ijbs.111636] [FullText] [Full Text(PDF)]
- 76 **Li W**, Huang X, Han X, Zhang J, Gao L, Chen H. IL-17A in gastric carcinogenesis: good or bad? *Front Immunol* 2024; **15**: 1501293 [RCA] [PMID: 39676857 DOI: 10.3389/fimmu.2024.1501293] [FullText] [Full Text(PDF)]
- 77 **Privitera G**, Williams JJ, De Salvo C. The Importance of Th2 Immune Responses in Mediating the Progression of Gastritis-Associated Metaplasia to Gastric Cancer. *Cancers (Basel)* 2024; **16**: 522 [RCA] [PMID: 38339273 DOI: 10.3390/cancers16030522] [FullText]
- 78 **Li CM**, Chen Z. Autoimmunity as an Etiological Factor of Cancer: The Transformative Potential of Chronic Type 2 Inflammation. *Front Cell Dev Biol* 2021; **9**: 664305 [RCA] [PMID: 34235145 DOI: 10.3389/fcell.2021.664305] [FullText] [Full Text(PDF)]
- 79 **Bockerstett KA**, Osaki LH, Petersen CP, Cai CW, Wong CF, Nguyen TM, Ford EL, Hofst DF, Mills JC, Goldenring JR, DiPaolo RJ. Interleukin-17A Promotes Parietal Cell Atrophy by Inducing Apoptosis. *Cell Mol Gastroenterol Hepatol* 2018; **5**: 678-690.e1 [RCA] [PMID: 29930985 DOI: 10.1016/j.jcmgh.2017.12.012] [FullText] [Full Text(PDF)]
- 80 **Li ML**, Hong XX, Zhang WJ, Liang YZ, Cai TT, Xu YF, Pan HF, Kang JY, Guo SJ, Li HW. Helicobacter pylori plays a key role in gastric adenocarcinoma induced by spasmodic polypeptide-expressing metaplasia. *World J Clin Cases* 2023; **11**: 3714-3724 [RCA] [PMID: 37383139 DOI: 10.12998/wjcc.v11.i16.3714] [FullText] [Full Text(PDF)]
- 81 **Yuan XY**, Zhang Y, Zhao X, Chen A, Liu P. IL-1 β , an important cytokine affecting Helicobacter pylori-mediated gastric carcinogenesis. *Microb Pathog* 2023; **174**: 105933 [RCA] [PMID: 36494022 DOI: 10.1016/j.micpath.2022.105933] [FullText]
- 82 **Zhou L**, Tang C, Li X, Feng F. IL-6/IL-10 mRNA expression ratio in tumor tissues predicts prognosis in gastric cancer patients without distant metastasis. *Sci Rep* 2022; **12**: 19427 [RCA] [PMID: 36371539 DOI: 10.1038/s41598-022-24189-3] [FullText]
- 83 **Kang JH**, Park S, Rho J, Hong EJ, Cho YE, Won YS, Kwon HJ. IL-17A promotes Helicobacter pylori-induced gastric carcinogenesis via interactions with IL-17RC. *Gastric Cancer* 2023; **26**: 82-94 [RCA] [PMID: 36125689 DOI: 10.1007/s10120-022-01342-5] [FullText] [Full Text(PDF)]
- 84 **Dewayani A**, Fauzia KA, Alfaray RI, Waskito LA, Doohan D, Rezkiha YAA, Abdurachman A, Kobayashi T, I'tishom R, Yamaoka Y, Miftahussurur M. The Roles of IL-17, IL-21, and IL-23 in the Helicobacter pylori Infection and Gastrointestinal Inflammation: A Review. *Toxins (Basel)* 2021; **13**: 315 [RCA] [PMID: 33924897 DOI: 10.3390/toxins13050315] [FullText] [Full Text(PDF)]
- 85 **Mozooni Z**, Ghadyani R, Soleimani S, Ahangar ER, Sheikhpour M, Haghighi M, Motallebi M, Movafagh A, Aghaei-Zarch SM. TNF- α , and TNFRs in gastrointestinal cancers. *Pathol Res Pract* 2024; **263**: 155665 [RCA] [PMID: 39442225 DOI: 10.1016/j.prp.2024.155665] [FullText]
- 86 **Hwang MA**, Won M, Im JY, Kang MJ, Kweon DH, Kim BK. TNF- α Secreted from Macrophages Increases the Expression of Prometastatic Integrin α V in Gastric Cancer. *Int J Mol Sci* 2022; **24**: 376 [RCA] [PMID: 36613819 DOI: 10.3390/ijms24010376] [FullText] [Full Text(PDF)]
- 87 **Hong JB**, Zuo W, Wang AJ, Lu NH. Helicobacter pylori Infection Synergistic with IL-1 β Gene Polymorphisms Potentially Contributes to the Carcinogenesis of Gastric Cancer. *Int J Med Sci* 2016; **13**: 298-303 [RCA] [PMID: 27076787 DOI: 10.7150/ijms.14239] [FullText] [Full Text(PDF)]
- 88 **Yu B**, de Vos D, Guo X, Peng S, Xie W, Peppelenbosch MP, Fu Y, Fuhler GM. IL-6 facilitates cross-talk between epithelial cells and tumor-associated macrophages in Helicobacter pylori-linked gastric carcinogenesis. *Neoplasia* 2024; **50**: 100981 [RCA] [PMID: 38422751 DOI: 10.1016/j.neo.2024.100981] [FullText]
- 89 **Liang P**, Zhang Y, Jiang T, Jin T, Chen Z, He F, Hu J, Yang K. Association between IL-6 and prognosis of gastric cancer: a retrospective study. *Therap Adv Gastroenterol* 2023; **16**: 17562848231211543 [RCA] [PMID: 38026103 DOI: 10.1177/17562848231211543] [FullText] [Full Text(PDF)]
- 90 **Oertli M**, Sundquist M, Hitzler I, Engler DB, Arnold IC, Reuter S, Maxeiner J, Hansson M, Taube C, Quiding-Järbrink M, Müller A. DC-derived IL-18 drives Treg differentiation, murine Helicobacter pylori-specific immune tolerance, and asthma protection. *J Clin Invest* 2012; **122**: 1082-1096 [RCA] [PMID: 22307326 DOI: 10.1172/JCI61029] [FullText]
- 91 **Lee SY**, Jhun J, Woo JS, Lee KH, Hwang SH, Moon J, Park G, Choi SS, Kim SJ, Jung YJ, Song KY, Cho ML. Gut microbiome-derived butyrate inhibits the immunosuppressive factors PD-L1 and IL-10 in tumor-associated macrophages in gastric cancer. *Gut Microbes* 2024; **16**: 2300846 [RCA] [PMID: 38197259 DOI: 10.1080/19490976.2023.2300846] [FullText] [Full Text(PDF)]
- 92 **Ge Y**, Janson V, Dong Z, Liu H. Role and mechanism of IL-33 in bacteria infection related gastric cancer continuum: From inflammation to tumor progression. *Biochim Biophys Acta Rev Cancer* 2025; **1880**: 189296 [RCA] [PMID: 40058506 DOI: 10.1016/j.bbcan.2025.189296] [Full Text]
- 93 **Petersen CP**, Meyer AR, De Salvo C, Choi E, Schlegel C, Petersen A, Engevik AC, Prasad N, Levy SE, Peebles RS, Pizarro TT, Goldenring JR. A signalling cascade of IL-33 to IL-13 regulates metaplasia in the mouse stomach. *Gut* 2018; **67**: 805-817 [RCA] [PMID: 28196875 DOI: 10.1136/gutjnl-2016-312779] [FullText]
- 94 **Liu X**, Ma Z, Deng Z, Yi Z, Tuo B, Li T, Liu X. Role of spasmodic polypeptide-expressing metaplasia in gastric mucosal diseases. *Am J Cancer Res* 2023; **13**: 1667-1681 [RCA] [PMID: 37293144] [FullText]

- 95 **Byrne J**, Baker K, Houston A, Brint E. IL-36 cytokines in inflammatory and malignant diseases: not the new kid on the block anymore. *Cell Mol Life Sci* 2021; **78**: 6215-6227 [RCA] [PMID: 34365521 DOI: 10.1007/s00018-021-03909-4] [FullText] [Full Text(PDF)]
- 96 **Zhang Y**, Liu Y, Guan X, Qu M, Wu D, Liu N, Lin Z, Liu Y, Wang H, Yang L. IL-36-related genes predict prognosis of gastric cancer. *Front Oncol* 2025; **15**: 1566993 [RCA] [PMID: 40606972 DOI: 10.3389/fonc.2025.1566993] [FullText] [Full Text(PDF)]
- 97 **Loe AKH**, Rao-Bhatia A, Wei Z, Kim JE, Guan B, Qin Y, Hong M, Kwak HS, Liu X, Zhang L, Wrana JL, Guo H, Kim TH. YAP targetome reveals activation of SPEM in gastric pre-neoplastic progression and regeneration. *Cell Rep* 2023; **42**: 113497 [RCA] [PMID: 38041813 DOI: 10.1016/j.celrep.2023.113497] [FullText]
- 98 **Garzon R**, Marcucci G, Croce CM. Targeting microRNAs in cancer: rationale, strategies and challenges. *Nat Rev Drug Discov* 2010; **9**: 775-789 [RCA] [PMID: 20885409 DOI: 10.1038/nrd3179] [FullText]
- 99 **Li D**, Zhang Y, Li Y, Wang X, Wang F, Du J, Zhang H, Shi H, Wang Y, Gao Y, Feng Y, Yan J, Xue Y, Yang Y, Zhang J. miR-149 Suppresses the Proliferation and Metastasis of Human Gastric Cancer Cells by Targeting FOXC1. *Biomed Res Int* 2021; **2021**: 1503403 [RCA] [PMID: 34957298 DOI: 10.1155/2021/1503403] [FullText] [Full Text(PDF)]
- 100 **Yang Y**, Nan Y, Du YH, Huang SC, Lu DD, Zhang JF, Li X, Chen Y, Zhang L, Yuan L. 18 β -glycyrrhetic acid promotes gastric cancer cell autophagy and inhibits proliferation by regulating miR-328-3p/signal transducer and activator of transcription 3. *World J Gastroenterol* 2023; **29**: 4317-4333 [RCA] [PMID: 37545635 DOI: 10.3748/wjg.v29.i27.4317] [FullText] [Full Text(PDF)]
- 101 **Min J**, Han TS, Sohn Y, Shimizu T, Choi B, Bae SW, Hur K, Kong SH, Suh YS, Lee HJ, Kim JS, Min JK, Kim WH, Kim VN, Choi E, Goldenring JR, Yang HK. microRNA-30a arbitrates intestinal-type early gastric carcinogenesis by directly targeting ITGA2. *Gastric Cancer* 2020; **23**: 600-613 [RCA] [PMID: 32112274 DOI: 10.1007/s10120-020-01052-w] [FullText]
- 102 **Chong Y**, Yu D, Lu Z, Nie F. Role and research progress of spasmolytic polypeptide-expressing metaplasia in gastric cancer (Review). *Int J Oncol* 2024; **64**: 33 [RCA] [PMID: 38299264 DOI: 10.3892/ijo.2024.5621] [FullText]
- 103 **Wang N**, Wu S, Zhao J, Chen M, Zeng J, Lu G, Wang J, Zhang J, Liu J, Shi Y. Bile acids increase intestinal marker expression via the FXR/SNAI2/miR-1 axis in the stomach. *Cell Oncol (Dordr)* 2021; **44**: 1119-1131 [RCA] [PMID: 34510400 DOI: 10.1007/s13402-021-00622-z] [FullText] [Full Text(PDF)]
- 104 **Cao Y**, Wang D, Mo G, Peng Y, Li Z. Gastric precancerous lesions: occurrence, development factors, and treatment. *Front Oncol* 2023; **13**: 1226652 [RCA] [PMID: 37719006 DOI: 10.3389/fonc.2023.1226652] [FullText]
- 105 **Chen WQ**, Tian FL, Zhang JW, Yang XJ, Li YP. Preventive and inhibitive effects of Yiwei Xiaoyu granules on the development and progression of spasmolytic polypeptide-expressing metaplasia lesions. *World J Gastrointest Oncol* 2021; **13**: 1741-1754 [RCA] [PMID: 34853647 DOI: 10.4251/wjgo.v13.i11.1741] [FullText] [Full Text(PDF)]
- 106 **Ke J**, Xu HE, Williams BO. Lipid modification in Wnt structure and function. *Curr Opin Lipidol* 2013; **24**: 129-133 [RCA] [PMID: 23348724 DOI: 10.1097/MOL.0b013e32835df2bf] [FullText]
- 107 **Xu W**, Kimelman D. Mechanistic insights from structural studies of beta-catenin and its binding partners. *J Cell Sci* 2007; **120**: 3337-3344 [RCA] [PMID: 17881495 DOI: 10.1242/jcs.013771] [FullText]
- 108 **Zuo W**, Yang H, Li N, Ouyang Y, Xu X, Hong J. Helicobacter pylori infection activates Wnt/ β -catenin pathway to promote the occurrence of gastritis by upregulating ASCL1 and AQP5. *Cell Death Discov* 2022; **8**: 257 [RCA] [PMID: 35538066 DOI: 10.1038/s41420-022-01026-0] [FullText] [Full Text(PDF)]
- 109 **Pang Q**, Tang Z, Luo L. The crosstalk between oncogenic signaling and ferroptosis in cancer. *Crit Rev Oncol Hematol* 2024; **197**: 104349 [RCA] [PMID: 38626848 DOI: 10.1016/j.critrevonc.2024.104349] [FullText]
- 110 **Koushyar S**, Powell AG, Vincan E, Pesses TJ. Targeting Wnt Signaling for the Treatment of Gastric Cancer. *Int J Mol Sci* 2020; **21**: 3927 [RCA] [PMID: 32486243 DOI: 10.3390/ijms21113927] [FullText] [Full Text(PDF)]
- 111 **Willett SG**, Lewis MA, Miao ZF, Liu D, Radyk MD, Cunningham RL, Bureclaff J, Sibbel G, Lo HG, Blanc V, Davidson NO, Wang ZN, Mills JC. Regenerative proliferation of differentiated cells by mTORC1-dependent paligenesis. *EMBO J* 2018; **37**: e98311 [RCA] [PMID: 29467218 DOI: 10.15252/embj.201798311] [FullText]
- 112 **Greicius G**, Kabiri Z, Sigmundsson K, Liang C, Bunte R, Singh MK, Virshup DM. PDGFR α (+) pericyptal stromal cells are the critical source of Wnts and RSPO3 for murine intestinal stem cells in vivo. *Proc Natl Acad Sci U S A* 2018; **115**: E3173-E3181 [RCA] [PMID: 29559533 DOI: 10.1073/pnas.1713510115] [FullText] [Full Text(PDF)]
- 113 **Sigal M**, Logan CY, Kapalczyńska M, Mollenkopf HJ, Berger H, Wiedenmann B, Nusse R, Amieva MR, Meyer TF. Stromal R-spondin orchestrates gastric epithelial stem cells and gland homeostasis. *Nature* 2017; **548**: 451-455 [RCA] [PMID: 28813421 DOI: 10.1038/nature23642] [FullText]
- 114 **Fischer AS**, Müllerke S, Arnold A, Heuberger J, Berger H, Lin M, Mollenkopf HJ, Wizeny J, Horst D, Tacke F, Sigal M. R-spondin/YAP axis promotes gastric oxyntic gland regeneration and Helicobacter pylori-associated metaplasia in mice. *J Clin Invest* 2022; **132**: e151363 [RCA] [PMID: 36099044 DOI: 10.1172/JCI151363] [FullText]
- 115 **Hoesel B**, Schmid JA. The complexity of NF- κ B signaling in inflammation and cancer. *Mol Cancer* 2013; **12**: 86 [RCA] [PMID: 23915189 DOI: 10.1186/1476-4598-12-86] [FullText] [Full Text(PDF)]
- 116 **Israël A**. The IKK complex, a central regulator of NF-kappaB activation. *Cold Spring Harb Perspect Biol* 2010; **2**: a000158 [RCA] [PMID: 20300203 DOI: 10.1101/cshperspect.a000158] [FullText]
- 117 **Zeng X**, Yang M, Ye T, Feng J, Xu X, Yang H, Wang X, Bao L, Li R, Xue B, Zang J, Huang Y. Mitochondrial GRIM-19 loss in parietal cells promotes spasmolytic polypeptide-expressing metaplasia through NLR family pyrin domain-containing 3 (NLRP3)-mediated IL-33 activation via a reactive oxygen species (ROS)-NRF2-Heme oxygenase-1(HO-1)-NF- κ B axis. *Free Radic Biol Med* 2023; **202**: 46-61 [RCA] [PMID: 36990300 DOI: 10.1016/j.freeradbiomed.2023.03.024] [FullText]
- 118 **Ding L**, Li Q, Chakrabarti J, Munoz A, Faure-Kumar E, Ocadiz-Ruiz R, Razumilava N, Zhang G, Hayes MH, Sontz RA, Mendoza ZE, Mahurkar S, Greenon JK, Perez-Perez G, Hanh NTH, Zavros Y, Samuelson LC, Iliopoulos D, Merchant JL. MiR130b from Schlafen4(+) MDSCs stimulates epithelial proliferation and correlates with preneoplastic changes prior to gastric cancer. *Gut* 2020; **69**: 1750-1761 [RCA] [PMID: 31980446 DOI: 10.1136/gutjnl-2019-318817] [FullText] [Full Text(PDF)]
- 119 **Shimizu T**, Choi E, Petersen CP, Noto JM, Romero-Gallo J, Piazzuelo MB, Washington MK, Peek RM Jr, Goldenring JR. Characterization of progressive metaplasia in the gastric corpus mucosa of Mongolian gerbils infected with Helicobacter pylori. *J Pathol* 2016; **239**: 399-410 [RCA] [PMID: 27125972 DOI: 10.1002/path.4735] [FullText]
- 120 **Dong J**, Cheng XD, Zhang WD, Qin JJ. Recent Update on Development of Small-Molecule STAT3 Inhibitors for Cancer Therapy: From Phosphorylation Inhibition to Protein Degradation. *J Med Chem* 2021; **64**: 8884-8915 [RCA] [PMID: 34170703 DOI: 10.1021/acs.jmedchem.1c01111] [FullText]

- 10.1021/acs.jmedchem.1c00629] [FullText]
- 121 **Zhang X**, Soutto M, Chen Z, Bhat N, Zhu S, Eissmann MF, Ernst M, Lu H, Peng D, Xu Z, El-Rifai W. Induction of Fibroblast Growth Factor Receptor 4 by Helicobacter pylori via Signal Transducer and Activator of Transcription 3 With a Feedforward Activation Loop Involving SRC Signaling in Gastric Cancer. *Gastroenterology* 2022; **163**: 620-636.e9 [RCA] [PMID: 35588797 DOI: 10.1053/j.gastro.2022.05.016] [FullText]
- 122 **Kitamura H**, Ohno Y, Toyoshima Y, Ohtake J, Homma S, Kawamura H, Takahashi N, Taketomi A. Interleukin-6/STAT3 signaling as a promising target to improve the efficacy of cancer immunotherapy. *Cancer Sci* 2017; **108**: 1947-1952 [RCA] [PMID: 28749573 DOI: 10.1111/cas.13332] [FullText] [Full Text(PDF)]
- 123 **El-Zaatari M**, Kao JY, Tessier A, Bai L, Hayes MM, Fontaine C, Eaton KA, Merchant JL. Gli1 deletion prevents Helicobacter-induced gastric metaplasia and expansion of myeloid cell subsets. *PLoS One* 2013; **8**: e58935 [RCA] [PMID: 23520544 DOI: 10.1371/journal.pone.0058935] [FullText] [Full Text(PDF)]
- 124 **Todisco A**. Regulation of Gastric Metaplasia, Dysplasia, and Neoplasia by Bone Morphogenetic Protein Signaling. *Cell Mol Gastroenterol Hepatol* 2017; **3**: 339-347 [RCA] [PMID: 28462376 DOI: 10.1016/j.jcmgh.2017.01.014] [FullText] [Full Text(PDF)]
- 125 **Gharibi T**, Barpour N, Hosseini A, Mohammadzadeh A, Marofi F, Ebrahimi-Kalan A, Nejati-Koshki K, Abdollahpour-Alitappeh M, Safaei S, Baghban E, Baradaran B. STA-21, a small molecule STAT3 inhibitor, ameliorates experimental autoimmune encephalomyelitis by altering Th-17/Treg balance. *Int Immunopharmacol* 2023; **119**: 110160 [RCA] [PMID: 37080068 DOI: 10.1016/j.intimp.2023.110160] [FullText]
- 126 **Zhao P**, Li J, Tian Y, Mao J, Liu X, Feng S, Li J, Bian Q, Ji H, Zhang L. Restoring Th17/Treg balance via modulation of STAT3 and STAT5 activation contributes to the amelioration of chronic obstructive pulmonary disease by Bufe Yishen formula. *J Ethnopharmacol* 2018; **217**: 152-162 [RCA] [PMID: 29454913 DOI: 10.1016/j.jep.2018.02.023] [FullText]
- 127 **Taylor NA**, Vick SC, Iglesia MD, Brickey WJ, Midkiff BR, McKinnon KP, Reisdorf S, Anders CK, Carey LA, Parker JS, Perou CM, Vincent BG, Serody JS. Treg depletion potentiates checkpoint inhibition in claudin-low breast cancer. *J Clin Invest* 2017; **127**: 3472-3483 [RCA] [PMID: 28825599 DOI: 10.1172/JCI90499] [FullText]
- 128 **Nguyen TL**, Khurana SS, Bellone CJ, Capoccia BJ, Sagartz JE, Kesman RA Jr, Mills JC, DiPaolo RJ. Autoimmune gastritis mediated by CD4+ T cells promotes the development of gastric cancer. *Cancer Res* 2013; **73**: 2117-2126 [RCA] [PMID: 23378345 DOI: 10.1158/0008-5472.CAN-12-3957] [FullText]
- 129 **Zhao R**, Cao G, Zhang B, Wei L, Zhang X, Jin M, He B, Zhang B, He Z, Bie Q. TNF+ regulatory T cells regulate the stemness of gastric cancer cells through the IL13/STAT3 pathway. *Front Oncol* 2023; **13**: 1162938 [RCA] [PMID: 37534250 DOI: 10.3389/fonc.2023.1162938] [FullText]
- 130 **Thiem S**, Eissmann MF, Elzer J, Jonas A, Putoczki TL, Poh A, Nguyen P, Preaudet A, Flanagan D, Vincan E, Waring P, Buchert M, Jarnicki A, Ernst M. Stomach-Specific Activation of Oncogenic KRAS and STAT3-Dependent Inflammation Cooperatively Promote Gastric Tumorigenesis in a Preclinical Model. *Cancer Res* 2016; **76**: 2277-2287 [RCA] [PMID: 26837764 DOI: 10.1158/0008-5472.CAN-15-3089] [FullText]
- 131 **Jin D**, Huang K, Xu M, Hua H, Ye F, Yan J, Zhang G, Wang Y. Deoxycholic acid induces gastric intestinal metaplasia by activating STAT3 signaling and disturbing gastric bile acids metabolism and microbiota. *Gut Microbes* 2022; **14**: 2120744 [RCA] [PMID: 36067404 DOI: 10.1080/19490976.2022.2120744] [FullText] [Full Text(PDF)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

