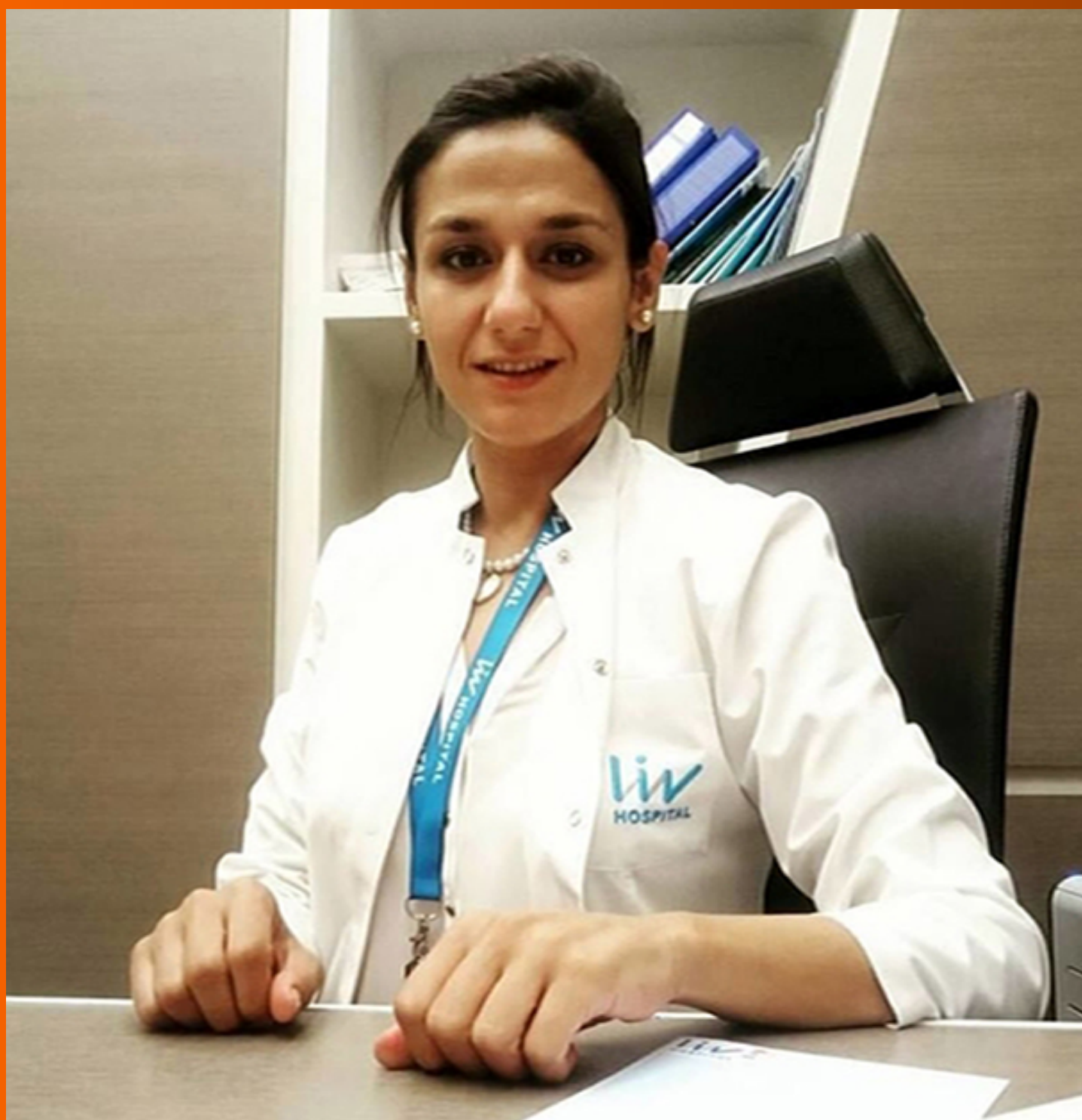


# World Journal of *Gastrointestinal Oncology*

*World J Gastrointest Oncol* 2019 October 15; 11(10): 768-932





### EDITORIAL

- 768 Cancer-specific metabolism: Promising approaches for colorectal cancer treatment  
*Jeong KY*

### REVIEW

- 773 Race, the microbiome and colorectal cancer  
*Royston KJ, Adedokun B, Olopade OI*
- 788 Targeted agents for second-line treatment of advanced hepatocellular carcinoma  
*Personeni N, Pressiani T, Bozzarelli S, Rimassa L*
- 804 Precision medicine in gastric cancer  
*Bonelli P, Borrelli A, Tuccillo FM, Silvestro L, Palaia R, Buonaguro FM*

### MINIREVIEWS

- 830 Endoscopic management of esophageal cancer  
*Ahmed O, Ajani JA, Lee JH*

### ORIGINAL ARTICLE

#### Basic Study

- 842 MicroRNA-320a suppresses tumor progression by targeting PBX3 in gastric cancer and is downregulated by DNA methylation  
*Li YS, Zou Y, Dai DQ*

#### Retrospective Study

- 857 Retrospective review of total neoadjuvant therapy  
*Babar L, Bakalov V, Abel S, Ashraf O, Finley GG, Raj MS, Lundeen K, Monga DK, Kirichenko AV, Wegner RE*
- 866 Evaluation of the safety and effectiveness of direct oral anticoagulants and low molecular weight heparin in gastrointestinal cancer-associated venous thromboembolism  
*Recio-Boiles A, Veeravelli S, Vondrak J, Babiker HM, Scott AJ, Shroff RT, Patel H, Elquza E, McBride A*

#### Retrospective Cohort Study

- 877 Fat clearance and conventional fixation identified ypN0 rectal cancers following intermediate neoadjuvant radiotherapy have similar long-term outcomes  
*Chen N, Sun TT, Li ZW, Yao YF, Wang L, Wu AW*

**Observational Study**

- 887** Acylcarnitine: Useful biomarker for early diagnosis of hepatocellular carcinoma in non-steatohepatitis patients  
*Takaya H, Namisaki T, Kitade M, Shimozato N, Kaji K, Tsuji Y, Nakanishi K, Noguchi R, Fujinaga Y, Sawada Y, Saikawa S, Sato S, Kawaratani H, Moriya K, Akahane T, Yoshiji H*

**META-ANALYSIS**

- 898** Prognostic and pathological impact of tumor budding in gastric cancer: A systematic review and meta-analysis  
*Guo YX, Zhang ZZ, Zhao G, Zhao EH*
- 909** Abnormally expressed circular RNAs as novel non-invasive biomarkers for hepatocellular carcinoma: A meta-analysis  
*Jiang YL, Shang MM, Dong SZ, Chang YC*

**CASE REPORT**

- 925** Gastric submucosa-invasive carcinoma associated with Epstein-Barr virus and endoscopic submucosal dissection: A case report  
*Kobayashi Y, Kunogi T, Tanabe H, Murakami Y, Iwama T, Sasaki T, Takahashi K, Ando K, Nomura Y, Ueno N, Kashima S, Moriichi K, Takei H, Fujiya M, Okumura T*

**ABOUT COVER**

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Naciye Cigdem Arslan, MD, Assistant Professor, Surgeon, Surgical Oncologist, General Surgery, Istanbul Medipol University, Esenler 34320, Istanbul, Turkey

**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 islet cell adenoma, liver cell adenoma, adenomatous polyposis coli, appendiceal neoplasms, bile duct neoplasms, biliary tract neoplasms, hepatocellular carcinoma, islet cell carcinoma, pancreatic ductal carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, hereditary nonpolyposis colorectal neoplasms, common bile duct neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

**INDEXING/ABSTRACTING**

The WJGO is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, and PubMed Central. The 2019 edition of Journal Citation Reports® cites the 2018 impact factor for WJGO as 2.758 (5-year impact factor: 3.220), ranking WJGO as 52 among 84 journals in gastroenterology and hepatology (quartile in category Q3), and 131 among 229 journals in oncology (quartile in category Q3).

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Li-Li Qi*  
Proofing Production Department Director: *Yun-Xiaojuan Wu*

**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, Rosa M Jimenez Rodriguez, Pashtoon Murtaza Kasi

**EDITORIAL BOARD MEMBERS**

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

**EDITORIAL OFFICE**

Jin-Lei Wang, Director

**PUBLICATION DATE**

October 15, 2019

**COPYRIGHT**

© 2019 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 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>



## Cancer-specific metabolism: Promising approaches for colorectal cancer treatment

Keun-Yeong Jeong

**ORCID number:** Keun-Yeong Jeong (0000-0002-4933-3493).

**Author contributions:** Jeong KY conceived the study and drafted the manuscript; This author approved the final version of the article.

**Conflict-of-interest statement:** This author has no conflicts of interest to declare.

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

**Manuscript source:** Invited manuscript

**Received:** July 17, 2019

**Peer-review started:** July 17, 2019

**First decision:** August 23, 2019

**Revised:** September 4, 2019

**Accepted:** September 10, 2019

**Article in press:** September 10, 2019

**Published online:** October 15, 2019

**P-Reviewer:** Luo HS

**S-Editor:** Dou Y

**L-Editor:** Filipodia

**E-Editor:** Qi LL

**Keun-Yeong Jeong**, The Research Center, Metimedi Pharmaceuticals, Incheon 22006, South Korea

**Corresponding author:** Keun-Yeong Jeong, PhD, Executive Vice President, The Research Center, Metimedi Pharmaceuticals, 263, Central-ro, Yeonsu-Gu, Incheon 22006, South Korea. [alvirus@naver.com](mailto:alvirus@naver.com)

**Telephone:** +82-32-2050541

**Fax:** +82-32-2050542

### Abstract

Investigation of cancer-specific metabolism has made it possible to establish the principle that atypically reconstituted metabolism is considered a hallmark of cancer due to changes in physiological property. Recently, a variety of targets depending on the prompted aerobic glycolysis process, starting from the abnormal uptake of glucose, and cancer-specific metabolism due to impaired mitochondrial function and abnormal expression of drug-metabolizing enzymes have been investigated and discovered. Given that most solid cancers rely on cancer-specific metabolism to support their growth, it is necessary to examine closely the specific processes of cancer metabolism and have a detailed understanding of how cellular metabolism is altered in colorectal cancer (CRC) related to CRC survival and proliferation. The development of key methods to regulate efficiently cancer-specific metabolism in CRC is still in the initial stage. Therefore, targeting cancer-specific metabolism will yield treatable methods that are critical as a new area of development strategies for CRC treatment.

**Key words:** Colorectal cancer; Cancer metabolism; Warburg effect; Aerobic glycolysis; Mitochondria metabolism

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Studies of cancer-specific metabolism have been conducted for over half a century, and the importance of promoting aerobic glycolysis, cancer favorable metabolic changes in mitochondria, and abnormal expression of drug-metabolizing enzymes has been emphasized through the established theories to date. Cancer-specific metabolism is a major theoretical background that can explain the process of survival and proliferation of most solid cancers. Developing cancer-specific metabolism-target drugs provide a novel treatable method that will be critical in this new area of treatment strategies for colorectal cancer. They have not yet been conquered and have infinite growth potential.





**Citation:** Jeong KY. Cancer-specific metabolism: Promising approaches for colorectal cancer treatment. *World J Gastrointest Oncol* 2019; 11(10): 768-772  
**URL:** <https://www.wjgnet.com/1948-5204/full/v11/i10/768.htm>  
**DOI:** <https://dx.doi.org/10.4251/wjgo.v11.i10.768>

## GENERAL VIEW ON CANCER METABOLISM

Cancer metabolism is classified as a classic but major research field in clinical and preclinical cancer biology. Studies on cancer-specific metabolism for over half a century have made it possible to establish the principle that abnormal metabolic changes are induced in normal cells<sup>[1]</sup>. This theory is primarily representative of the imbalance between the expression of oncogenes and the regulation of tumor suppressor genes, and these changes support the induction and maintenance of malignant characteristics in cancer cells<sup>[2]</sup>. Atypically reconstituted metabolism is considered a hallmark of cancer due to changes in a physiological property that are most commonly found in cancer cells<sup>[2]</sup>. Main issues while approaching the study of cancer metabolism are how abnormal functions in cancer-specific metabolism contribute to the survival of cancer cells and how to change these metabolisms using certain targets. The comprehensive principle of cancer metabolism is that altered metabolic activity improves the adaptability of cells to provide a selective benefit for tumorigenesis<sup>[3]</sup>. Well-known theories indicate that activities initiated by abnormal metabolic changes support cancer cell survival under stress conditions, such as hypoxic environment<sup>[3]</sup>. This is an important characteristic of malignant cancer metabolism and enables the abnormal proliferation of cancer cells<sup>[4]</sup>.

Most solid cancers, including colorectal cancer (CRC), have inherent but similar metabolic characteristics. A well-known cancer-specific metabolism is the Warburg effect, and aerobic glycolysis has been well-established as a main metabolic feature of cancer cells<sup>[4,5]</sup>. This theory states that an increase in aerobic glycolysis is a physiological response to hypoxia and that cancer cells absorb a large quantity of glucose and produce lactate regardless of the oxygen supply, providing a secondary path that meets the metabolic needs of the cancer cells<sup>[1,4]</sup>. However, this well-established theory does not fully reflect cancer-specific metabolism. Although the Warburg effect has led to the widely held conception that cancer cells rely only on aerobic glycolysis to manage their major source of energy, the function of the mitochondria is not completely inactivated even under hypoxic environment<sup>[6]</sup>. In addition, the role of drug-metabolizing enzymes (DMEs) in anti-cancer drug resistance should also be noted. Therefore, when studying cancer-specific metabolism, not only should aerobic glycolysis be considered but also abnormal mitochondrial metabolism and DMEs in cancer cells.

## TARGETABLE CANCER-SPECIFIC METABOLISM IN AEROBIC GLYCOLYSIS

Abnormal uptake of glucose is the most well-known metabolism in cancer<sup>[5]</sup>. Glucose transporter (GLUT) is a unique transporter and is considered responsible for a large amount of glucose uptake in cancer cells<sup>[5]</sup>. The expression of GLUT1 is increased in cancer cells among several subtypes of GLUT, and there is an alternative glucose uptake with passive GLUT, GLUT3, which is not expressed in most normal cells<sup>[7]</sup>. Following a large amount of glucose uptake, many enzymes involved in the process of producing pyruvate from glucose can be targeted. These include hexokinase 2, which produces glucose-6-phosphate from glucose, and phosphofructokinase 2, which produces fructose-6-phosphate from fructose-2, 6-bisphosphate<sup>[8]</sup>. The pyruvate kinase M2 isoform, which promotes aerobic glycolysis and produces pyruvate from phosphoenolpyruvate, is one of the important target proteins expressed by aerobic glycolysis<sup>[9]</sup>. Activation of the listed targets above led metabolism in cancer cells to produce a large amount of pyruvate from the excess glucose uptake. In normal cells, pyruvate is converted to acetyl-CoA *via* pyruvate dehydrogenase and generates energy through oxidative phosphorylation (OXPHOS)<sup>[6]</sup>. However, in cancer cells, pyruvate dehydrogenase kinase is activated, and pyruvate dehydrogenase is phosphorylated by pyruvate dehydrogenase kinase to suppress its activity. Excess pyruvate that cannot participate in OXPHOS is converted from pyruvate and NADH to lactate and NAD<sup>+</sup> by lactate dehydrogenase A<sup>[6]</sup>. Then, the symbiotic relationship

between cancer cells following lactate production must be considered. There are cancer cells that release lactate through the monocarboxylate transporter and cancer cells that utilize the released lactate as an energy source. Therefore, to target lactate dehydrogenase A and monocarboxylate transporters involved in the producing and transferring lactate would be important<sup>[6,10]</sup>.

## TARGETABLE CANCER-SPECIFIC METABOLISM IN MITOCHONDRIA

Cancer cells accommodate to hypoxic condition by converting their metabolism to the oxygen-independent system by mitochondria<sup>[11]</sup>. Reductive carboxylation is induced in mitochondria under hypoxic condition, this feature is a driving force that maintains the viability by having tolerance about hypoxia<sup>[12,13]</sup>. These specific regulations in mitochondrial metabolism cause multiple changes in the composition of electron transport chain complexes, which could decrease O<sub>2</sub>-dependent mitochondrial function, such as coupled metabolism with OXPHOS<sup>[14]</sup>. However, this metabolic change does not represent a complete loss of mitochondrial function. Instead of OXPHOS, which is referred to as the tricarboxylic acid cycle, mitochondria carry out cancer-specific metabolism adapting to the hypoxic condition for cancer survival<sup>[6]</sup>. Point mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2 involve the production of d-2hydroxyglutarate (2HG), which is an inhibitor of  $\alpha$ -ketoglutarate-dependent dioxygenase<sup>[15]</sup>. Since  $\alpha$ -ketoglutarate-dependent dioxygenase is involved in the oxygen-sensing pathway that mediates the destabilization of hypoxia-inducible factor, the abnormal state of mitochondrial IDH and 2HG contributes to hypoxia-inducible factor stability and the transcriptional activation for expression of cancer favorable factors, such as vascular endothelial growth factor and GLUT<sup>[16]</sup>.

Cancer favorable mitochondria can lead to lipid synthesis, amino acid synthesis, and nucleotide synthesis critical for cancer survival<sup>[17]</sup>. These diverse syntheses depend on the reverse metabolism of glutamine in cancer favorable mitochondria, and it replenishes the biosynthetic precursors<sup>[18]</sup>. Glutaminase catalyzes the conversion of glutamine to glutamate in a pathway involved in producing citrate<sup>[19]</sup>. Since glutaminase 1 is a source of 2HG production by mutated IDH1, it mediates the entry of glutamine into mitochondria and can thus enhance the proliferation of cancer cells<sup>[16,17,19]</sup>. Therefore, although mitochondria under hypoxic condition have a diminished function of energy metabolism, it should also be important to explore a variety of pathways that produce energy sources for cancer survival through changes in the cancer-specific metabolism in mitochondria by genetic variation or glutamine.

## TARGETABLE CANCER-SPECIFIC METABOLISM IN DMES

Despite advances in medicine that lead to new drugs with specific molecular targets, major problems still remain with regard to anticancer drug resistance. This resistance is known to be caused by certain proteins that are attributed to DMES in cancer, and DMES can influence the susceptibility to therapeutic effects<sup>[20]</sup>. DMES are classified in neoplastic tissues as phase I and phase II. Cytochrome P450-dependent monooxygenase (CYP) and dihydropyrimidine dehydrogenase (DPD), which are included in phase I enzymes, lead to the variations of efficacy or toxicity of the anticancer drugs<sup>[21]</sup>. Members of the subfamily of cytochrome P450 are represented to CYP family 1-3 (CYP1-3)<sup>[21]</sup>. Phase II enzymes mediate the conjugation of the products from phase I metabolism resulting in the subsequent elimination step of drug metabolism<sup>[22]</sup>. Glucuronide, glutathione system, beta-glucuronidase, aldehyde dehydrogenase, and nicotinamide adenine dinucleotide phosphate hydrogen quinone oxidoreductase-1 are members belonging to the phase II enzymes<sup>[22]</sup>. In CRC, it has been reported that CYP1B1, DPD, uridine diphospho-glucuronosyltransferase, and glutathione-transferase were highly expressed as compared to normal tissues<sup>[20,23]</sup>. Increase in such DMES can induce resistance to various anticancer agents, in particular to cisplatin, paclitaxel, docetaxel, flutamide, and mitoxantrone, including 5-fluorouracil and irinotecan, which belong to the first or second line regimens for the CRC treatment<sup>[20]</sup>. The following mechanisms relating to DMES expression have not been clearly elucidated. It can be explained either by metabolism of anticancer drugs and elimination of their action or by direct deactivation of drug molecules and mitogen-activated protein kinase pathways<sup>[20,23]</sup>. Further, several attempts have been made to develop potent inhibitors of DMES, however many of these have been found to have a poor safety profile and to have many side effects<sup>[20,23]</sup>. Therefore, while focusing on molecular biological factors aimed at the intrinsic metabolism involved in growth and

metastasis, there is a continuing need to clarify the metabolism of DMEs, particularly by CYP1B1, DPD, uridine diphospho-glucuronosyltransferase, and glutathione-transferase, as a strategy overcoming cancer drug resistance.

## THERAPEUTIC APPLICABILITY TARGETING CRC

Given that most solid cancers rely on cancer-specific metabolism to support their growth, survival, and multi-organ metastasis, targeting these metabolic activities may be main therapeutic strategies against CRC. In addition, the characteristic liver metastasis of CRC is also closely related to the metabolic abnormalities; therefore, the therapeutic and inhibitory effects on metastasis through targeting cancer-specific metabolism can be potentially anticipated. As described in the previous paragraphs, since various factors relating to cancer-specific aerobic glycolysis, mitochondrial metabolism, and DMEs have been identified in recent years, the stage has been reached where an optimal strategy to suppress effectively these metabolism-based targets should be established. A detailed understanding of how cellular metabolism is altered in CRC that leads to cancer progression and metastasis will provide insight into which proteins represent promising targets in CRC therapy, which will be raised from the analysis of cancer-specific metabolism. Building a theoretical context to understand metabolic regulation in CRC, however, remains a challenge for the successful construction of strategies. Therefore, the specific process of cancer metabolism related to the survival and differentiation of CRC must be closely examined, and work must focus to advance steadily the discovery of candidate proteins that can target it. It is important to point out that with the exception of 5-fluorouracil, Gemcitabine, or Pemetrexed, which were developed for inhibiting nucleic acid synthesis, other developing therapies are only in the early stages, where most pre-clinical studies have been completed<sup>[20]</sup>. Of course, it is not my purpose to raise concerns that there are few attempts to target cancer-specific metabolism for the treatment of CRC but to emphasize that the development of key methods to regulate efficiently cancer-specific metabolism is still under the initial stage. Thus, it is suggested that developing cancer-specific metabolism-target drugs provide a novel treatable method that will be critical in this new area of treatment strategies for CRC. They have not yet been conquered and have infinite growth potential.

## REFERENCES

- 1 Kim SY. Cancer metabolism: strategic diversion from targeting cancer drivers to targeting cancer suppliers. *Biomol Ther (Seoul)* 2015; **23**: 99-109 [PMID: 25767677 DOI: 10.4062/biomolther.2015.013]
- 2 Fouad YA, Aanei C. Revisiting the hallmarks of cancer. *Am J Cancer Res* 2017; **7**: 1016-1036 [PMID: 28560055]
- 3 Asgari Y, Zabihpour Z, Salehzadeh-Yazdi A, Schreiber F, Masoudi-Nejad A. Alterations in cancer cell metabolism: the Warburg effect and metabolic adaptation. *Genomics* 2015; **105**: 275-281 [PMID: 25773945 DOI: 10.1016/j.ygeno.2015.03.001]
- 4 Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009; **324**: 1029-1033 [PMID: 19460998 DOI: 10.1126/science.1160809]
- 5 Lu J, Tan M, Cai Q. The Warburg effect in tumor progression: mitochondrial oxidative metabolism as an anti-metastasis mechanism. *Cancer Lett* 2015; **356**: 156-164 [PMID: 24732809 DOI: 10.1016/j.canlet.2014.04.001]
- 6 Zheng J. Energy metabolism of cancer: Glycolysis versus oxidative phosphorylation (Review). *Oncol Lett* 2012; **4**: 1151-1157 [PMID: 23226794 DOI: 10.3892/ol.2012.928]
- 7 Calvo MB, Figueroa A, Pulido EG, Campelo RG, Aparicio LA. Potential role of sugar transporters in cancer and their relationship with anticancer therapy. *Int J Endocrinol* 2010; **2010** [PMID: 20706540 DOI: 10.1155/2010/205357]
- 8 Li XB, Gu JD, Zhou QH. Review of aerobic glycolysis and its key enzymes - new targets for lung cancer therapy. *Thorac Cancer* 2015; **6**: 17-24 [PMID: 26273330 DOI: 10.1111/1759-7714.12148]
- 9 Luo W, Semenza GL. Pyruvate kinase M2 regulates glucose metabolism by functioning as a coactivator for hypoxia-inducible factor 1 in cancer cells. *Oncotarget* 2011; **2**: 551-556 [PMID: 21709315 DOI: 10.18632/oncotarget.299]
- 10 Keenan MM, Chi JT. Alternative fuels for cancer cells. *Cancer J* 2015; **21**: 49-55 [PMID: 25815843 DOI: 10.1097/PPO.0000000000000104]
- 11 Semenza GL. Regulation of metabolism by hypoxia-inducible factor 1. Proceedings of the Cold Spring Harbor symposia on quantitative biology. *Cold Spring Harb Sym* 2011; **76**: 347-353 [DOI: 10.1101/sqb.2011.76.010678]
- 12 Luft R, Landau BR. Mitochondrial medicine. *J Invest Med* 1995; **238**: 405-421 [DOI: 10.1111/j.1365-2796.1995.tb01218.x]
- 13 Kim JA, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. *Circ Res* 2008; **102**: 401-414 [PMID: 18309108 DOI: 10.1161/CIRCRESAHA.107.165472]
- 14 Fuhrmann DC, Brüne B. Mitochondrial composition and function under the control of hypoxia. *Redox Biol* 2017; **12**: 208-215 [PMID: 28259101 DOI: 10.1016/j.redox.2017.02.012]
- 15 Losman JA, Kaelin WG. What a difference a hydroxyl makes: mutant IDH, (R)-2-hydroxyglutarate, and



- cancer. *Genes Dev* 2013; **27**: 836-852 [PMID: [23630074](#) DOI: [10.1101/gad.217406.113](#)]
- 16 **Böttcher M**, Renner K, Berger R, Mentz K, Thomas S, Cardenas-Conejo ZE, Dettmer K, Oefner PJ, Mackensen A, Kreutz M, Mougiakakos D. D-2-hydroxyglutarate interferes with HIF-1 $\alpha$  stability skewing T-cell metabolism towards oxidative phosphorylation and impairing Th17 polarization. *Oncoimmunology* 2018; **7**: e1445454 [PMID: [29900057](#) DOI: [10.1080/2162402X.2018.1445454](#)]
- 17 **Ahn CS**, Metallo CM. Mitochondria as biosynthetic factories for cancer proliferation. *Cancer Metab* 2015; **3**: 1 [PMID: [25621173](#) DOI: [10.1186/s40170-015-0128-2](#)]
- 18 **DeBerardinis RJ**, Mancuso A, Daikhin E, Nissim I, Yudkoff M, Wehrli S, Thompson CB. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. *Proc Natl Acad Sci U S A* 2007; **104**: 19345-19350 [PMID: [18032601](#) DOI: [10.1073/pnas.0709747104](#)]
- 19 **Choi YK**, Park KG. Targeting Glutamine Metabolism for Cancer Treatment. *Biomol Ther (Seoul)* 2018; **26**: 19-28 [PMID: [29212303](#) DOI: [10.4062/biomolther.2017.178](#)]
- 20 **Pathania S**, Bhatia R, Baldi A, Singh R, Rawal RK. Drug metabolizing enzymes and their inhibitors' role in cancer resistance. *Biomed Pharmacother* 2018; **105**: 53-65 [PMID: [29843045](#) DOI: [10.1016/j.biopha.2018.05.117](#)]
- 21 **Nebert DW**, Gonzalez FJ. P450 genes: structure, evolution, and regulation. *Annu Rev Biochem* 1987; **56**: 945-993 [PMID: [3304150](#) DOI: [10.1146/annurev.bi.56.070187.004501](#)]
- 22 **Iyanagi T**. Molecular mechanism of phase I and phase II drug-metabolizing enzymes: implications for detoxification. *Int Rev Cytol* 2007; **260**: 35-112 [PMID: [17482904](#) DOI: [10.1016/S0074-7696\(06\)60002-8](#)]
- 23 **Michael M**, Doherty MM. Tumoral drug metabolism: overview and its implications for cancer therapy. *J Clin Oncol* 2005; **23**: 205-229 [PMID: [15625375](#) DOI: [10.1200/JCO.2005.02.120](#)]



Published By Baishideng Publishing Group Inc  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
Telephone: +1-925-2238242  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

