Responses to the reviewer's comments

Manuscript NO: 50139

Article title: Cancer-specific metabolism: Promising approaches for colorectal cancer treatment

First of all, I would like to thank all editors and an expert reviewer for the constructive comments on my manuscript. I sincerely prepared a separate reference list, point by point, to response comments.

Reviewer's comments:

Reviewer code: 03656586

[Specific comments to author]

Tumor cells form a unique metabolic pattern during the growth process - the Warburg effect, in which the glucose in the tumor cells rarely enters the high-efficiency metabolic capacity mode of the Krebs cycle, but most of them undergo anaerobic mode. Glycolysis rapidly metabolizes to form lactic acid. The Warburg effect not only makes the endogenous metabolism of cells change drastically, but also the expression and activity of drug metabolizing enzymes (DMEs) related to the metabolism of exogenous substances. The special living environment and metabolic patterns of tumor cells, as well as changes in the expression and activity of intracellular DMEs, inevitably cause the metabolic intensity and elimination rate of drugs in tumor cells to be different from those in normal cells, directly affecting the target cells in tumor cells. Exposure and efficacy, as well as exposure and toxicity in normal tissue cells.

Author's response: I agree. Different mechanisms of resistance of cancer cells as compared to normal cells have become a major pitfall in cancer chemotherapy. This theory importantly includes drug-metabolizing enzymes (DMEs).

This article has a systematic description in this file, so that we basically understand the mechanism of metabolic abnormalities in colon cancer cells. In addition, it should be noted that liver metastasis of colon cancer is also closely related to metabolic abnormalities.

Author's response: Following the reviewer's comment, a related paragraph was added to emphasize the association between metabolic abnormalities and liver metastasis.

"Given that most solid cancers rely on cancer-specific metabolism to support their growth, survival, and multi-organ metastasis, targeting these metabolic activities may assistant and main therapeutic strategies against in the CRC. In addition, the characteristic liver metastasis of colorectal cancer 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."

Through this article, we can understand the metabolic abnormalities of colon cancer, know: 1. Some specific DMEs expression in colon cancer tissue can be used as tumor markers; 2. Some enzyme-dependent metabolic reactions can be applied to tumor targeted therapy; Certain specific metabolic reactions mediated by DMEs expressed in colon cancer tumors can be used for screening for anticancer drugs. 4. To understand the mechanism of chemotherapy resistance of colon cancer at the metabolic level.

Author's response: Depending on the reviewer's suggestion, a new paragraph introducing promising targets for DMEs in colorectal cancer has been additionally organized.

"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, therefore DMEs can influence the susceptibility to therapeutic effects [1]. DMEs are classified in neoplastic tissues as phase I and phase II. Cytochrome (CYP) P450-dependent mono-oxygenase (P450) and dihydropyrimidine dehydrogenase (DPD), which are included in phase I enzymes, lead to the variations of efficacy or toxicity of the anticancer drugs [2]. Members of the subfamily of cytochrome P450 are represented to CYP1, CYP2, and CYP3 [2]. Phase II enzymes mediate the conjugation of the products from phase I metabolism resulting in the subsequent elimination step

of drug metabolism [3]. Glucuronide, glutathione system, beta-glucuronidase, aldehyde dehydrogenase, and nicotinamide adenine dinucleotide phosphate hydrogen quinone oxidoreductase-1 are members belonging to the phase II enzymes [3]. In CRC, it has been reported that CYP1B1, DPD, uridine diphospho-glucuronosyltransferase (UGT), and glutathione-transferase (GST) were highly expressed as compared to normal tissues [1, 4]. 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 [1]. The following mechanisms relating to DMEs expression have not been clearly elucidated. It can only be explained to a simple flow with the context of being involved in the metabolism of anticancer drugs for eliminating their action, or with the context of direct deactivation of drug molecules and mitogen-activated protein kinase pathways [1, 4]. Further, several attempts have been made to develop potent inhibitors of DMEs, however many of these have been found to have poor safety profile and to have many side effects in clinical [1, 4]. 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 CYP1B1, DPD, UGT, and GST, as a strategy overcoming cancer drug resistance."

References

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