

August 18, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12408-review.doc).

**Title:** p53 mutations in colorectal cancer- molecular pathogenesis and pharmacological reactivation

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**Name of Journal:** *World Journal of Gastroenterology*

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

(1) Figure 1 and 2 has been redrawn with authors' original conceptions and now they are numbered as new Figure 1 and 3 because a new Figure 2 which recapitulates how miRNA regulates p53, is made.

(2) A new Table 2 has been added to illustrate the important affection of p53, especially its mutation and over-expression, in the adenoma-carcinoma progression of CRC.

(3) We have highlighted p53 mutations in sporadic CRC in the text. This review paper focuses on p53 mutations in sporadic CRC only.

Hereditary CRC consists of familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), which are respectively 3-5% and 5-10% in CRC.

FAP is an autosomal dominant hereditary disease, which leads to a large number of colorectal adenomas in early stage, then progresses to adenocarcinoma eventually without any treatments. Deletion of Adenomatous polyposis coli (APC) gene on chromosome 5q21 is responsible for FAP.

HNPCC is also known as Lynch syndrome, another autosomal dominant hereditary disease. Germline mutations in mismatch repair (MMR) genes renders increase in the genetic predisposition to CRC and other cancers, such as gastric cancer, endometrial carcinoma, etc.

(4) We modified the Figure1B. Now it recaps the interactions of p53 in the different cellular pathways (i.e., apoptosis, cell cycle arrest and senescence pathways).

(5) Page numbers have been added in word file of the manuscript.

(6) The third sentence in the paragraph 5.1.1 has been changed and the number of the paragraph entitled RITA was corrected to 5.1.3.

(7) We provide further explanation for acquire secondary resistance. Drug resistance can be classified into *primary* resistance and *secondary* resistance (also called as *acquired* resistance). *Primary* resistance refers to the patient's lack of efficacy of the drug at the beginning of the treatment. *Secondary* resistance means the drug achieves complete or partial response at the initial phase of treatment; however, the drug loses its efficacy after a period of treatment. In other word, the patient acquires resistance to the drug after some time treatment. This acquired resistance happens often when a single drug used for a prolonged period. A variety of mechanisms account for acquired resistance, including mutations of oncogene or tumor suppressor gene, change of cellular metabolic pathway,

overexpression of certain enzymes. However, when a few different drugs are used in combination to target different pathways or mechanisms, it will reduce the chance of secondary resistance occurring. In clinic either in anti-cancer or anti-microbacteria fields, doctors often prescribe combination therapy, i.e., a few drugs used together.

(8) A write error in little captions: "6.1.3 RITA" has been changed to "5.1.3 RITA".

3. The corresponding author (Chng WJ) would like to clarify that English is my native language. In this setting, we asked permission for not engaging a professional English editing company.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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