Response to Reviewers' Comments:

1. In abstract, authors should describe the spelling of abbreviation such as GD, CRC and MRD.
Response: Thanks for the reviewer's advice. We have described the spelling of all the abbreviation in the "Abstract" of the revised manuscript.

2. *MDR should be used as only gene name MDR1, not used for abbreviation of multidrug resistance.*
Response: Thanks for the reviewer's advice. It is indeed easy to confuse MDR with MDR1. However, MDR was extensively used for multidrug resistance but not for MDR1 gene. To distinguish MDR and MDR1 more clearly, we use "MDR phenotype" in the manuscript. Many papers use MDR as the abbreviation of multidrug resistance even in their titles. For example:

1) **Cell Death Dis. 2015 Dec 17;6:e2020. doi: 10.1038/cddis.2015.363.**
2) **Cancer Lett. 2016 Jun 28;376(1):118-26. doi: 10.1016/j.canlet.2016.03.030.**
3) **Cancer Med. 2016 Mar 25. doi: 10.1002/cam4.694. [Epub ahead of print]**
4) **Biochim Biophys Acta. 2016 Mar;1860(3):618-27. doi: 10.1016/j.bbagen.2015.12.011.**
5) **Biomed Pharmacother. 2015 Aug;74:49-56. doi: 10.1016/j.biopha.2015.07.001.**
6) **BMC Cancer. 2015 May 6;15:358. doi: 10.1186/s12885-015-1361-3.**
7) **PLoS One. 2015 Jun 22;10(6):e0127841. doi: 10.1371/journal.pone.0127841.**
8) **J Natl Cancer Inst. 2015 Mar 11;107(5). pii: djv046. doi: 10.1093/jnci/djv046.**

3. Authors described the GD condition as 1.5 mmol/l glucose. So glucose concentration of normal condition should be described in materials and methods section, too.
Response: Thanks for the reviewer's advice. In "materials and methods" section, we have added the glucose concentration of normal condition.

4. In figure 1b, F-FU should be revised. If authors describe the apoptotic rate as %, please check the number. Moreover, if authors used annexin V to evaluate apoptotic cell, please show the data of FACS. If not, the legend should be revised.
Response: We greatly thank reviewer for the professional advice and apologize for our incorrect presentation. We have changed the number of apoptotic rate as % in figure 1B，and the same mistake has been corrected in figure 3B (as shown in new figure 1 and new figure 3).

5. In figure3c, apoptotic induction by anticancer drug is weak. Authors should show the data of no treatment and chemo-treated data in normal condition as control.
Response: Thanks for the reviewer's suggestion. The GD is a stress condition for cells and DNA transfection also influence the cell status, so we chose relative low concentration of anticancer drugs to induce apoptosis. Actually, we had use higher concentrations of anticancer drugs in our preliminary tests, and observed that most of cells died under the combined treatments (GD, DNA transfection and drugs). The apoptosis included the early and late apoptosis assessed by annexin V and 7-ADD staining, respectively; and the total apoptotic ratio is not very low (as shown in figure 1). We have detected the apoptotic ratio of LoVo cells with or without chemo-treatment under normal condition (as shown in figure 2).

Figure 1

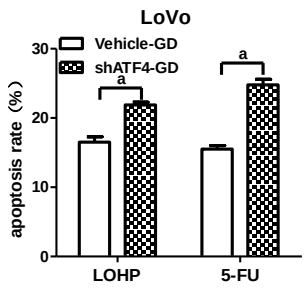
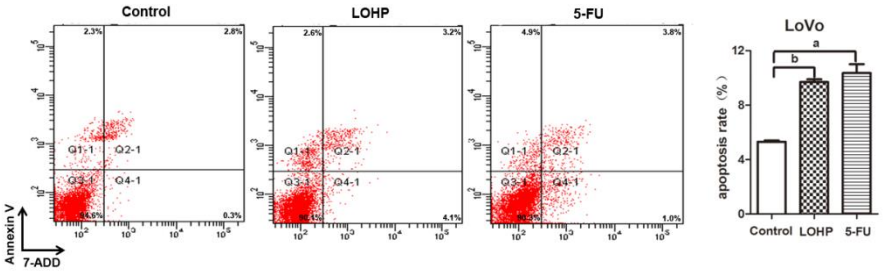


Figure 2



6. In figure3 legend, authors described the MDR1 expression using RT-PCR, however, the data was not shown.

Response: We thank the reviewer for pointing out this. We have added the data of the MDR1 expression using RT-PCR in the new figure 3D.

7. In figure4, please clarify what cells were used in Figure 4 legend.

Response: Thanks for the reviewer's advice. In figure 4, LoVo-ATF4 cells were used in all experiments. We have added the information in the legend of figure 4.

8. Validation of ATF4 overexpression and suppression by WB should be shown in figure5 as main data. Figure 4d or Figure5 should include the mock and transfectant with and without chemo-treatment.

Response: Thanks for the reviewer's professional advices. We had detected the overexpression and suppression of ATF4 by WB assay, and the results have been added in the new figure 5. We also detected MDR1 protein in mock and transfectant cells without chemo-treatment by WB, but no bands were observed even the loading total protein as high as 100 ug. We further detected the mRNA levels of MDR1 by qRT-PCR, and observed that shATF4 did knockdown the expression of MDR1 in mock and transfectant cells without chemo-treatment, but Ct value were more than 33 cycle. These data suggest the very weak expression of MDR1 in CRC cells without drug treatment (as shown in table 1).

Table 1

	actin-Ct	MDR1-Ct
LoVo-ATF4-Vehicle	15.184	33.247
	15.277	33.509
LoVo-ATF4-shATF4	15.625	35.270
	15.499	35.563
LoVo-ATF4-Vehicle	14.993	33.479
	15.134	33.423
LoVo-ATF4-shATF4	15.673	35.773
	15.655	35.292

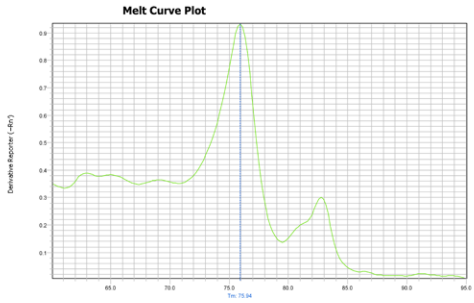
9. pGipZ might be better to be revised as mock or vehicle in the figures.

Response: Thanks for the reviewer's advices. pGipZ was revised as vehicle in all figures and the revised manuscript.

10. *In figure2b, authors should explain what was treated in these cells. Moreover, authors described the p-PERK induction by GD, however, mRNA level of PERK as strongly induced by GD. Why the total PERK was not enhanced by GD in figure2b. Please explain this difference.*

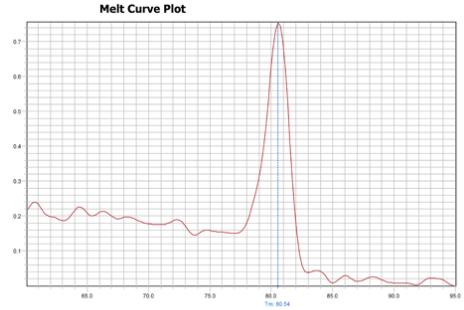
Response: We thank reviewer for pointing out these. Actually, LoVo, HCT116, HT29 and DLD1 cells were used in our preliminary study. Following the reviewer's suggestion, we have deleted the results of HT29 and DLD1 cells in figure 2B to maintain the consensus through the study. We have checked the initial data, and found the results of PERK PCR nonspecific (as shown in figure 3). Therefore, we redetected the expression of PERK under improved PCR conditions and did not observe significant difference between two groups, which was similar with that of our previous study (Cancer Res 2012; 72: 5396-5406). We have deleted results of PERK mRNA in figure 2A.

Figure 3



PERK-nonspecific

Figure 4



PERK-specific