Author’s response to reviews

Title: Computational analysis of receptor tyrosine kinase inhibitors and cancer metabolism: Implications for treatment and discovery of potential therapeutic signatures

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Version: 1 Date: 30 Jan 2019

Author’s response to reviews:

BCAN-D-18-02898: Computational analysis of receptor tyrosine kinase inhibitors and cancer metabolism: Implications for treatment and discovery of potential therapeutic signatures

Dear Dr. Charles Theillet,

Thank you for your response and reviewers comments. We have modified the manuscript “BCAN-D-18-02898: Computational analysis of receptor tyrosine kinase inhibitors and cancer metabolism: Implications for treatment and discovery of potential therapeutic signatures” in response to the extensive and insightful reviewer comments and addressed all the changes recommended by the reviewers. To this effect the text was revised to focus on key points and conclusions.

Below please find a point-by-point response to each comment provided by both reviewers with reference to the section of the revised manuscript where applicable.
We hope that these revisions are sufficient for the approval of the article for publication in BMC Cancer and are looking forward to your feedback.

Yours sincerely,

Dr. Jian Li

Reviewer 1.

1. While authors claimed that "The results reveal the strength of multiple-cancer analysis over conventional signature-based analysis on a single cancer type”, there is no convincing clear data to substantiate that claim. They still focused on individual cancers like breast citing the higher incidence.

Answer:

The combined analysis of multiple cancer types is becoming increasingly important (Rosario et al., 2018, Nat. Commun [PubMed:30552315]; Chen et al., 2018, Cell [PubMed:29625054]). In this study, we used a single method and model to demonstrate the metabolic impact on multiple cancer types as described in the first paragraph of the result section. In the following paragraphs within this section, we further focused on data from single cancer types, however comparing these results with those of multiple-cancer in order to demonstrate the advantages of this type of comparison. Uncovering common characteristics to all of the studied cancer types may uncover underlying similarities and indicate common treatment strategies.

2. Authors have suggested to better understand the cross talk between signaling and metabolic pathways. It is unclear how this study helps in that direction. Computational metabolic models have been developed to integrate information but have not been discussed here.

Answer:

Understanding the crosstalk between cancer cell signaling and metabolic pathways may offer new and previously unstudied targets for treatment. In this study we addressed this point, for instance, in page 5 line 4, the crosstalk between c-Met, ALK signaling and metabolic pathways was addressed. In addition on page 5 line 27, the connection between IP3 signaling and inositol-phosphate metabolic pathways and on page 7 line 40, the connection between purine- and pyrimidine pathways and signaling pathways such as EGFR were focused on. While the study does focus on cancer metabolomics, the observed effects are discussed according to available literature that describes subsequent effects on cell signaling.
3. Claim to discover 'metabolic therapeutic signature; is not well supported by the results. How are the two figures useful in therapy of breast and CNS cancer?

Answer:

The figures have been revised for the new version of the manuscript. We recreated all figures and added several new ones to better illustrate the results according to the reviewer comments.

Reviewer 2.

1. A figure describing the workflow to identify the metabolic impact and signature would be helpful for the readers to clearly understand the analysis performed.

Answer:

Thank you for this insightful comment. According to this comment we added a paragraph titles “The aim, design and setting of this study” at the beginning of the Materials and Methods section in the revised version. In addition we added the new figure 1 to visualize the workflow of this study.

2. The authors selected 8 drugs, but they should explain the rational of this selection.

Answer:

In the same paragraph “The aim, design and setting of this study” in the Materials and Methods section in this revised version we explained the rational of these 8 drugs selection. Namely, the RTK inhibitors tested within the CCLE were used.

3. This article aims to « focus on the possible impact of RTK inhibitors on the cancer metabolism », as it can be « antagonistic or agonistic during or after treatment ». To specifically address this question, authors should mention the main applications of these drugs (e.g : erlotinib used to treat lung cancer, etc), it would give a more clinical aspect to this article. This could be added to the Table 1.

Answer:

According to the reviewers suggestion, we updated the table 1 and added one column to address the tumor types where these drugs are used as part of the clinical treatment in the revised version of manuscript.

4. In line with the previous comment, in the sections dealing about breast, liver/pancreas, and CNS cancer, the metabolic effect of the drug(s) generally used to treat these types of cancers should be more precisely discussed. Indeed, this is the direct application of this
work and it is surprisingly less developed, it would reinforce the clinical perspective of the analysis conducted here. In addition, erlotinib is essentially used to treat lung cancer, and this type of cancer is particularly difficult to manage considering the high rate of new cases and mortality. It would be interesting to characterize the metabolic pathways affected by this drug in the lung cancer cell lines of the CCLE.

Answer:

Thank you again for this insightful comment, in order to address this issue, we modified the respective paragraphs in the results section: 1. “The Metabolic Impact and Signature of RTK Inhibitor in Breast Cancer” and 2. “The Relationship between Metabolic Signatures of Liver and Pancreatic Cancer”. Furthermore, we created a new paragraph in the result section titled “The Metabolic Impact of RTK Inhibitor in Lung Cancer Cell Lines” to characterize the metabolic effect of drug treatments in lung cancer cell lines. We also recreated figure 2, 3, and 4 to better display the content of this section.

5. In the section dealing about breast cancer, and also elsewhere, authors talk about « high impact on metabolism pathway » or « highly affected metabolic components ». From this point of view it is hard to assess whether this impact corresponds to an increase of the metabolism pathway or whether a decrease of the metabolism pathway. This point should be clarified to more precisely understand the effect of the mentioned drugs on the corresponding metabolic pathway.

Answer:

We added a paragraph to the end of the discussion of the manuscript to address this point. And thanks you again to the reviewer for this comment.

6. In the section dealing about CNS, authors say that « L2HGDH gene may be an indication of treatment outcome ». This is confusing since a genetic alteration or a gene expression deregulation may be informative on treatment outcome, not the gene by itself.

Answer:

The statement from the reviewer is correct, we indeed meant the expression level of this gene as an indicator of treatment outcome. We corrected this issue in the page 7 line 12 in the revised manuscript with track-back information.

7. Background section, mTOR should not be listed as a tyrosine kinase receptor.

Answer:

This statement was corrected in the revised manuscript.