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To: Editor-in-Chief, Editorial Office

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Title: Downregulation of miRNA-21 and Cancer Stem Cells after Chemotherapy results in better outcome in Breast Cancer patients

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Dear editor,

Thank you so much for your email letter informing us your decision and reviewer's comments. We are very much encouraged the comments from you and the reviewers. We think the reviewers comment and constructive and useful for improving the quality of our manuscript. We have taken all comments seriously and made a thorough revision. The entire article has undergone re-editing and extensive proofreading in order to maintain the scientific meaning as well as the English language quality. Please find our point to point correspondence below.

A revised manuscript was uploaded on your website. Please feel free to let me know if you have any further questions. Thanks again.

Best Regards,

Shailendra Dwivedi

Reviewer comment1: This is a wonderful letter about cancer epigenetics. After learning the latest research of Mandhair HK et al., the authors made a brief introduction and present some personal opinions on autophagy, post-transcriptional regulation and cancer stem cells in cancer. They also showed an interesting result that miR-21 expression was declined after three cycles of chemotherapy in breast cancer. This letter may provide clues for further study on cancer epigenetics in the future.

Authors Response1: Thank you for your kind words, as well as for the recommendation to explore epigenetics in the future.

Reviewer Comment 2. In abstract, it is mentioned "combination therapy with anti-miRNA21/mimic miRNA21 may prove beneficial for cancer management". Why might mimic miRNA21 also be used in cancer therapy? Please give a brief introduction of possible benefit of mimic miRNA.

Authors Response 2: Thank you for asking about mimic miRNAs, which we have not discussed in depth. These corrections have also been added to the colored text. We believe that the miRNA21 mimic study should also be conducted prior to planning translational research. The mimic-miRNAs are chemically synthesized duplexes that are designed to activate only one miRNA strand. It is often used to overexpress miRNA transiently and to augment endogenous microRNA activity for investigating gain or loss of function. In conjunction with microRNA and gene expression profiles, miRNA mimics and inhibitors may be tested for their role in identifying specific microRNA-gene relationships.

Several genes can be affected by a single microRNA, which is well established. They may, for instance, contribute to the expression of proteins that are essential for normal biochemical reactions and physiological functions, or they may contribute to the development of diseases. In order to achieve therapeutic success, mimic-miRNA-based in vivo and in vitro studies must be performed to explore all possible target sites. Thus, miRNA-mimics-based studies can provide a complete understanding. It is thus possible to unravel the whole scenario of gene targets just by increasing the targeted oligonucleotides (miRNA mimics).

Reviewer Comment 3: In the last paragraph, it is mentioned "the regulation in autophagy by modulating epigenetic milieu (Methylation, and non-coding RNA) transcriptional factors, and Cancer Stem Cells (CSCs) may help in providing better cancer management". Autophagy regulated by CSCs is not easy to understand, which can be supplemented in the previous paragraphs.

Authors Response 3: Regarding our article on autophagy regulation prospects, we appreciate the thoughtful comment you made on the aspect of CSCs (Cancer Stem Cells). The article has also been updated to include it. Autophagy plays a context-dependent role in the development of cancer. Further, recent findings lend support to the hypothesis that the CSC microenvironment can intriguingly regulate autophagy. Cells of malignant tumors, for example, induce autophagy in the microenvironment to increase the availability of recycled nutrients to support their own growth. Autophagy inhibition within the tumor has moderate effects on tumor progression through modulation of essential signaling pathways or by promoting resistance to chemotherapy, while autophagy inhibition through chloroquine oral administration reduces tumor growth and invasion more noticeably. Cancer (Cancer Stem Cells) regulates autophagy in vivo, but its exact role in tumor growth remains unclear. Recently, a study in the animal model of Drosophila melanogaster malignant tumors confirmed that autophagy is induced within the tumor microenvironment and distant tissues. It also reported that metabolically stressed tumor cells trigger autophagy through Drosophila tumor necrosis factor and interleukin-6-like signals.