Reviewer's report

Title: Epigenetic silencing of miR-375 induces trastuzumab resistance in HER2-positive breast cancer by targeting IGF1R

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Reviewer: Bolin Liu

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General comments:

This study aims to determine the basis of IGF-1R upregulation in trastuzumab-resistant breast cancer cells. Mechanistically, upregulation of IGF-1R in the resistant cells is due to the epigenetic silencing of a tumor suppressive miRNA, miR-375 which has been shown to target IGF-1R mRNA. The inverse correlation of miR-375 expression and IGF-1R mRNA levels has also been identified in clinical samples of breast cancer patients. The results implicate miR-375 as a potential target in combination with trastuzumab for the treatment of HER2-positive breast cancer. The information included would be very interesting to those investigators who are exploring the mechanisms of trastuzumab resistance.

Minor Essential Revisions:

1. On page 14, it says “Next, we investigated whether miR-375 suppresses trastuzumab resistance and metastasis by targeting IGF1R.” However, there is no study related to tumor metastasis. And the following sentence “Concurrent with the expression pattern of miR-375, IGF1R protein and mRNA levels were lower in trastuzumab-resistant cells than parental SKBr-3 cells (Figure 3A).” is a wrong statement.

2. Fig. 2B, the legend in “Parental” is wrong.

3. Herceptin induced substantial apoptosis in the parental SKBR3 cells (fig. 2D) and BT474 and MDA-MB-453 cells (fig. 2G). These data are not in agreement with a number of literatures indicating that Herceptin mainly inhibits cell proliferation via induction of cell cycle G1 arrest without apoptosis.

4. It is not clear whether the clinical samples used in fig. 3D are from all breast cancers or HER2-positive breast cancers.

5. Fig. 4C shows survival curves with Kaplan-Meier analysis in the animal studies. What does the data mean?

6. The quality of western blot data (fig. 3A and fig. 5E) needs to be improved.

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.