Reviewer's report

Title: A Her2-let-7-beta2-AR circuit affects prognosis in patients with Her2-positive breast cancer

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Reviewer: Antimo Migliaccio

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The paper by Liu et al. described a cross talk between Her2 and #2 adrenergic receptor (#2-AR). In detail they observe that over-expression of Her2 in breast cancer cell line MCF-7 (MCF-7/Her2) represses the expression of microRNA let-7f, which, in turn, down regulates baseline #2-AR expression. The MEK1 inhibitor PD98059 restores the let-7f level, suggesting that Her2-overexpression-mediated ERK constitutive activation inhibited let-7f, leading to the up regulation of the #2-AR expression. The transfection with the let-7f mimics down regulated the #2-AR level, whereas the let-7 inhibitor significantly up regulated the #2-AR expression in both parental MCF-7 and MCF-7/Her2 cells. On the other hand, treatment of MCF-7/Her2 cells with isoproterenol also reduced decreased let-7f expression, demonstrating a synergistic effect of Her2 over expression and on #2-AR activation in down regulating let-7f. Furthermore they observe that high level of #2-AR associates with lymph node metastasis and poor outcome in the patients with Her2-positive breast cancer.

This a quite interesting article as identifies #2-AR as new marker of clinical outcome of breast cancer. The findings are also consistent with the view that stress can worsen the outcome of human cancers. nevertheless it raises some questions. In example whereas it is known that let-7f controls #2-AR expression by interacting with the gene encoding for this receptor, it is not completely clear the mechanism by which Her2 activate ERK and #2-AR pathway regulate let-7f expression.

As concerns the experimental findings the effect of let-7f mimics on #2-AR expression is rather poor. I would suggest presenting a different more impressive experiment. A quantification of WB bands a statistical analysis of the data shown in Fig. 2 would be appropriate.

The mechanism of #2-AR expression inhibition could be verified by ChIP experiments.

The role of the ERK pathway relies only on the effect of PD98,059. It should be confirmed by some other experimental finding. PI3-K is also downstream Her2: I am also wondering what is the effect of LY294002 on let7-f expression

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