Author's response to reviews

Title: Autocrine Regulation of Cell Proliferation by Estrogen Receptor-alpha in Estrogen Receptor-alpha-positive Breast Cancer Cell Lines

Authors:

Huining Tan (htan1@uvm.edu)
Yili Zhong (yzhong@uvm.edu)
Zhongzong Pan (zpan@uvm.edu)

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Author's response to reviews:

Dear editor:

Since this is a manuscript rejected by the BCR, I would like to take this opportunity to highlight a few things why we felt this manuscript is worthy of being published.

1) Although it is believed that there should be autocrine regulation in some primary breast carcinomas and the ERalpha-positive cell lines, we did not find any literature that directly address the question. We did not find any publication that showed that ERalpha is colocalized with the cell proliferation marker in MCF-7, T47D, and ZR75-1 cells. We kindly felt that the question of autocrine regulation is taken for granted.

2) In the studies from the literature, the function of ERalpha in cell cycle progression was evaluated mostly using synchronized cells. To our knowledge, all the synchronization methods lead to loss of detectable ERalpha. In our studies, we found that high levels of ERalpha are found in all phases of the cell cycle. This finding indicates that the results from the synchronized cells might only addressed some of the ERalpha functions, ERalpha at high levels at different cell cycle phases might have some new function(s).

3) The deranged expression pattern of ERalpha during cell cycle progression also raises the question whether the co-location of ERalpha and Ki-67 is just a coincidence rather than an evidence for the autocrine regulation. To address this question, we provided evidence that activation of ERalpha in G1 phase does lead cell cycle progression through the different phases and the data collectively support the autocrine action of ERalpha.

4) Another point is that ERalpha is colocalizaed with Ki-67 in all the three cell lines we evaluated. In the primary breast carcinomas, the ERalpha(+) tumors with colocalization of ERalpha and Ki-67 is really limited and for those with colocalization the percentage of cells with colocalization varies widely from a few percent to sometimes 80+ percent. In other words, many ERalpha-positive
primary tumors may not use the autocrine regulation. The knowledge from the studies using these ERalpha-positive cell lines (with autocrine regulation) may not apply to all the ERalpha-positive primary tumors.

Thank you for considering our manuscript.

Sincerely,
Zhongzong Pan, PhD
Assistant Professor
Department of Animal Science
University of Vermont
570 Main Street
Burlington, VT 05405
Phone: (802)656-0134; (802)656-5888
FAX: (802)656-8196
Email: zpan@uvm.edu