Reviewer’s report

Title: Leptin-induced ER-Positive Breast Cancer Cell Viability and Migration is mediated by Suppressing CCN5-Signaling via Activating JAK/AKT/STAT-pathway

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Reviewer: Laundette Jones

Reviewer's report:

Overall, these experiments are straightforward and seem reasonable. However, there is weakness in the attention to detail regarding why CCN5 was pursued in ER positive breast cancer. The overall data is interesting, however the final figure is a bit misleading and is too narrowly focused. CCN5 may be a key player, but it needs to be placed in context with other key protein players in the field. As I mentioned in my comments below, other labs have looked at the role of leptin in ER positive breast cancer. I strongly suggest the authors review the literature and place their protein of interest in context with the work in the field. Otherwise, this work stands alone and it is hard for readers to appreciate the significance of this work in light of what has already been done and how this work may help to move the field forward. Once this work is placed into context with other work in the field, the authors may find that other experiments may be needed to provide a more comprehensive perspective.

Other comments are provided below:

1. Could use more clarification in the background of why CCN5 was investigated:

The author's state that "the primary aim of the present study was to evaluate whether leptin has any influence on CCN5 to promote BC progression". However, the rationale provided in the Background section for pursuing the direction to investigate the role of CCN5 is quite abrupt and could use a description that provides a better transition on why CCN5 was chosen to pursue out of all the other candidates (e.g. is this work completely exploratory? Has any other papers reported on CCN5 or is this the first paper to do so?)

Actually, some of the information in the discussion section would be more appropriately placed in the intro section. For example on page 16 it states- "Multiple studies from our laboratory and others have shown that CCN5-signaling plays a vital role in orchestrating the growth and behavior of cancer cells. CCN5 acts as an anti-invasive 3 element in cancer cells of the breast, pancreas and GI tract. [29-31, 50, 61, 62]. CCN5 is a 29-35 kDa secreted protein and is overexpressed in preneoplastic disorders in the human breast, including atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS) compared with adja- cent invasive cancer cells where expression levels were undetected, minimally detected, or only sporadically detected [29]." I would've preferred to see this at the beginning
2. Experiments are straightforward and seem reasonable. However, it is not clear how/why 50ng/ml was the only dose chosen for Leptin. Is there a dose response? Is this the standard concentration used for prior studies?

Notes on References:

1. I thought it was rather odd and very unclear to me why the authors would select the very "specific" research article (ref. 1) to support the "general "statement in the background section.

General statement: Breast cancer (BC) is the most commonly occurring cancer and second most common cause of cancer deaths among American women [1].


2. The manuscript lacks inclusion of the more recent articles highlighting research on leptin and estrogen positive breast cancer, for example:


The majority of the articles cited are prior to 2010. The authors should make sure that their literature search in the background is current.

Leptin-regulated gene expression in MCF-7 breast cancer cells: mechanistic insights into leptin-regulated mammary tumor growth and progression
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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