Reviewer's report

Title: IL-6 signaling between ductal carcinoma in situ cells and carcinoma-associated fibroblasts mediates tumor cell migration

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Reviewer: Chanitra Thuwajit

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The manuscript entitled “IL-6 signaling between ductal carcinoma in situ cells and carcinoma-associated fibroblasts mediates tumor cell migration” by Osuala KO et al.

The authors showed the importance of cancer-associated fibroblasts (CAFs) in the promotion of DCIS breast cancer via the secreted pro-inflammatory cytokines in particular IL-6. The MAME model was the key method utilized in this study for the studying of CAFs and cancer cells interactions in 3D fashion. The results showed the positive induction capability of CAFs to induce DCIS cancer cell proliferation and migration through IL-6 secreted from CAFs, but not cancer cells. The manuscript was well designed and the using of 3D-MAME model of cell culture made the result interesting and eligible to translate to what happen in the patients.

Major Compulsory Revisions

1. In Figure 1, the author revealed that IL-6 was up-regulated expressed in DCIS in comparison to that in normal breast tissues. The enrolled cases in this study was denoted as 61. It is more related to the in vitro results if the authors can analyze these 61 cases for the clinicopathological correlations with the level of IL-6 expression from IHC grading. For example, whether the patients with high level of IL-6 have big tumor mass, and/or increased incidence of cancer invasion or metastasis, and survival time? The patient demographic data should be presented.
The suitable statistical analyses (i.e. univariate analysis, multivariate analysis, Kaplan-Meier log rank test) should be used to show the statistical significance of each parameter.

2. The IHC results in Figure 1 exhibited the increased expression of IL-6 in not only fibroblasts but also cancer cells. These depict the potential that microenvironmental IL-6 in breast cancer DCIS may be released from both cancer cells and stromal fibroblasts. However, the in vitro study revealed that only knockdown of IL-6 in fibroblast could abrogate the migration of cancer cells, while this effect could not be observed when knockdown IL-6 in DCIS cancer cells. The author should explain why in the discussion part.

Minor Essential Revisions
1. In page 5, line 80-83, the author should explain what the cancer cells used in the study are including MCF10A, MCFA0.DCIS, WS-12TI, SUM102; and which tissues that the primary fibroblasts (CAF40TKi, NAF98i, FB-NF, NAF-FB, FB-CAF) were derived from? Especially the CAFs, the author should confirm that they were fibroblasts isolated from the DCIS tissues.
2. In Figure 1, the scale bars should be presented in the IHC pictures.
3. Why in the result Figure 3, the authors used CAF40TKi to compare with FB-NF, why not NAF98 or NAF-FB?

Level of interest: An article whose findings are important to those with closely related research interests

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.