Reviewer’s report

Title: Lipid Raft Disruption by Cholesterol Depletion Attenuates Migration, Invasion and Angiogenesis by Downregulation of uPAR and MMP-9 in Breast Carcinoma Cells

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Reviewer: Hideki Yamaguchi

Reviewer’s report:

In this study the authors investigate the effect of lipid raft disruption by cholesterol depletion on migration, invasion, and angiogenesis in two breast cancer cell lines, MDA-MB-231 and ZR751. The authors demonstrate that disruption of lipid rafts by cholesterol depletion inhibits the activity, expression, and localization of uPA, uPAR, and MMP-9, and downregulates several signaling pathways involving Src, FAK, Cav, ERK, and PI3K/Akt. The authors further demonstrated that cholesterol depletion blocks migration, invasion, and angiogenic activity of breast cancer cells. This manuscript contains interesting new observations, such as the inhibition of spheroid invasion and angiogenesis by cholesterol depletion. Overall, this manuscript is suitable for publication in BMC cancer. However, I have a few issues that should be addressed before publication.

Major points

1. Fig. 2A and B upper panels, MMP-9 staining images: It is difficult to judge colocalization of MMP-9 with GM1, because the signals for MMP-9 are saturated in these images. The authors should provide better images to show their colocalization.

2. Fig. 1, 2, 4, and 5: The authors provide several bar graphs, in which the relative values are represented in arbitrary unit. It would be better to set the control value to 100% and then show the relative values. Additionally, it is unclear how the relative values were calculated or the absolute values were normalized in these graphs. In particular, in Fig. 5A and C, the values for untreated should be set to 100% for each sample, because each antibody has different titer and therefore it is not reasonable to compare the signals between different antibodies.

Minor points

1. Materials and Methods: The methods for cell culture and determination of cellular cholesterol levels are missing.

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