Reviewer's report

Title: Increased Diacylglycerol Kinase zeta Expression in Human Metastatic Colon Cancer Cells Contributes to Enhanced Invasion by Augmenting Rho GTPase Activity

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Reviewer: Matthew Topham

Reviewer's report:

In this manuscript, the authors used a paired set of cell lines isolated from either a primary colorectal cancer or its lymph node metastasis to study the role of DGK zeta in metastasis. Based on their prior data showing that DGK zeta modulates cell migration in fibroblasts and published data demonstrating that the mRNA for this DGK was elevated in the metastatic cell line, they hypothesized that high levels of DGK zeta would enhance RhoA and Rac1 activity and contribute to the migratory potential of the metastatic line. Consistent with their hypothesis, they find elevated DGK zeta protein in the metastatic line and show that shRNA-mediated knockdown of DGK zeta reduces the elevated levels of active Rac1 and RhoA in the metastatic line. Functionally, these changes lead to reduced migration of the cells. The question posed by the authors is well defined, the methods are appropriate and well described, and the data are sound. Additionally, the conclusions are supported by the data and the work builds upon their prior work and adds relevance to it. Thus, the work is solid and relevant and has numerous strengths. However, there are two weaknesses that should be addressed prior to publishing.

Minor Essential Revisions:
1. The clinical relevance of the work is diminished by their use of a single cell line and lack of correlative clinical data such as evaluation of primary and metastatic tumor specimens. Evaluating additional cell lines and tumor specimens would significantly strengthen the manuscript. But to my knowledge, other matched colorectal cell lines don’t exist and clinical specimens are precious and difficult to come by. So these experiments would be very hard to complete. Given this reality, the authors should at least acknowledge these limitations of their work in the discussion section of the manuscript.

2. The functional data using shRNA knockdown is limited to a single clonal cell line. Ideally, this should be shown in a second clonal cell line as well. However, the data derived from the line that they studied are entirely consistent with their prior work and with the signaling data presented in the manuscript. Given these internal consistencies, I don’t feel that additional experiments should be completed. But again, the authors should indicate this limitation in their discussion.
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