Reviewer's report

Title: CD155/PVR plays a key role in cell motility during tumor cell invasion and migration

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Reviewer: Igor Roninson

Reviewer's report:

General
This is the second paper describing the results of a novel functional-proteomics screening system, which was developed by these authors and recently published as a major article in Nature Cell Biology. The analysis described in the present manuscript confirms the power of this methodology in the analysis of tumor cell invasion and shows that this approach identifies known proteins involved in this process (integrin beta1) as well as novel players (CD155). CD155 has been identified as the poliovirus receptor but its cellular function had been unknown at the time of this study (although a role for CD155 in cell adhesion has been suggested in a very recent paper by Oda et al., referenced by the authors). In the present manuscript, Jay and colleagues describe a series of experiments that convincingly document the role of CD155 in the invasion, motility and morphology of HT1080 fibrosarcoma cells, with the motility role confirmed in a glioblastoma cell line. They also show that CD155 expression is common in many different cancers, suggesting its potential role in tumor invasion. CD155 therefore may be viewed as a novel potential target for the development of anti-metastatic drugs.

There are, however, several issues that the authors need to address before the paper can be recommended for publication.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. On the experimental side, the most essential negative control in all the FALI experiments is scFv 1A2, which is described in the Methods section as “a control surface binder” but not explained anywhere else in the text or in the figure legends. This control should provide the evidence that cell invasion and migration are not affected by non-specific irreversible binding of a bulky scFV or Ab ligand to the cell surface. The authors should either show or describe the reactivity of 1A2 with the surface of HT1080 and U87MG cells relative to CD155 binders, to assure that this is an adequate control. Also why is this control not included in Fig. 1A (the invasion assay)?

2. In regard to the interpretation, the authors state in the Abstract and elsewhere that CD155 is “upregulated” in cancer cell lines and primary tumors. However, they have not compared CD155 expression between tumors and normal tissue samples of the same patients and do not appear to have analyzed multiple samples of each normal tissue. The authors clearly show that CD155 is expressed (but not necessarily upregulated) in a substantial number of cancers, and their conclusions should be worded accordingly.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

3. The authors also state in the Introduction and the Discussion that CD155 is “required” for tumor
cell invasion and migration, but in such a case its inactivation or knockdown should have completely or mostly abolished these activities, rather than decreased them by 20-30%, as observed in this study. It would be more appropriate to say that this protein is “involved” in invasion and migration.

Discretionary Revisions (which the author can choose to ignore)

4. The authors have shown the expression of CD155 at the leading edge of cells in the wound-healing assay. Surprisingly, they do not say whether FALI or knockdown of this protein affect the rate of wound healing. Have they attempted such measurements?

5. It would have been very informative if the authors interrogated the available SAGE and microarray databases for CD155 expression in normal and tumor tissues, supplementing their own protein expression assays.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

None