Reviewer’s report

Title: Desmoglein 2 is a novel substrate of kallikrein 7 in pancreatic cancer

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Reviewer: Martyn Chidgey

Reviewer’s report:

General

In this paper the authors build on their previous finding that the serine protease kallikrein 7 (hK7) is over-expressed in pancreatic cancer. They show that expression of the desmosomal glycoproteins Dsg1 and Dsg2 is reduced in pancreatic adenocarcinomas, that recombinant Dsg1 and Dsg2 are degraded in vitro by hK7 and that expression of hK7 in cultured cells results in shedding of the Dsg2 extracellular domain. Based on their data they hypothesise that Dsg2 is a novel substrate of hK7 in pancreatic cancer, and that loss of Dsg2 could result in reduced adhesion and so facilitate invasion. The paper is very well written and the experimental data appear to be of high quality (although somewhat limited in scope). The data would be more convincing if a larger number of pancreatitis/cancer samples had been analysed, and if loss of adhesion following shedding of the Dsg2 extracellular domain could be established in their cell culture model system.

Major compulsory revisions

1. Figure 3. I would like to see what happens to a protein that is not a substrate for hK7 (e.g. BSA?) under the same conditions. How do we know that Dsg1 and Dsg2 are not being degraded in this experiment simply as a result of excessive amounts of enzyme?

2. Figure 5. I would like to see (or at the very least be told) what happens to the cells that express hK7 and shed sDsg2. According to the authors hypothesis one might expect to see loss of adhesion in these cells and perhaps some change in their morphology/behaviour. If no such change is seen some explanation/discussion of why not should be included in the text. Furthermore as it stands the figure implies that #3 is different from Vec at p < 0.05. What about #7?

3. Figure 4. I accept that the authors assayed the samples prior to loading but I would still like to see loading controls (e.g. actin?) included in this figure.

4. I think that the title of the article is over-stated and should be changed.

Minor essential revisions

1. Results, paragraph 1. I do not know what a ‘desmoplastic response’ is.

2. Discussion, paragraph 1. Desmocollins, desmogleins and plakoglobin are not
sufficient to produce an intact functional desmosome – desmoplakin and plakophilin are also required.

3. Discussion, paragraph 3. The discussion relating to novel DSG1 genes is confusing and should be rewritten (or omitted?).

Discretionary revisions

1. For the sake of completeness it would be nice to know whether hK7 is able to release sDsg1 from cultured cells – perhaps by co-transfecting Dsg1 and hK7 into the same cell line.

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