Reviewer's report

Title: Met-Independent Hepatocyte Growth Factor-mediated regulation of cell adhesion in human prostate cancer cells

Version: 1 Date: 26 May 2006

Reviewer: Paula Kaplan-Lefko

Reviewer's report:

General

Summary

The authors have described experimental data to suggest that HGF induced cell spreading involves nucleolin independent of c-Met in C4-2 prostate cancer cells. They have shown that neutralization of HGF using an anti-HGF antibody reduces cell spreading in C4-2 cells. They have further shown that HGF increased cell spreading specifically on a laminin substrate. The authors suggest that HGF enhances cell spreading but inhibits cell migration. They claim that c-Met expression is absent in C4-2 cells, and therefore, HGF is acting in a c-Met independent manner. They further show that signals downstream of c-Met are not activated following HGF stimulation. The authors have immunoprecipitated HGF in HGF stimulated C4-2 cells and have shown that nucleolin is pulled down with HGF whereas c-Met was not detectable. The authors argue that these data suggest that HGF interacts with nucleolin on the cell surface in a c-Met independent manner to promote spreading of C4-2 cells.

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

1) While the data are potentially very interesting, the manuscript is poorly written which makes it difficult to interpret data and to follow the flow of ideas.

2) The authors suggest that HGF enhances cell spreading but decreases migration. This does not seem consistent with the function of HGF in motility and migration. The migration data that is shown in Figure 3a and 3b is somewhat confusing. In Figure 3a, it appears that the cells are migrating whereas the text and Figure 3b says that migration is inhibited. This needs to be clarified. In addition, the authors seem to use the terms cell adhesion and cell spreading interchangeably. These definitions need to be clarified.

3) The authors suggest that C4-2 and LNCaP cells express no c-Met, however, there is a low level of c-Met expressed by RT-PCR in Figure 4a although no c-Met was detected by western in Figure 4b. This would suggest that c-Met may be expressed at very low levels that are not detectable by western. Therefore, it is not quite accurate to state that the effects observed are independent of c-Met.

4) There is data to show that integrins are involved in HGF effects on cell spreading. It is not clear what the link is between HGF, integrins and nucleolin. The relationship needs to be expanded in the discussion and perhaps include a model for the proposed interactions.

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

1) Immunoprecipitation of HGF pulled down 2 proteins. One was sequenced and determined to be nucleolin. The other protein â€œlikely represents HGF itselfâ€ although it was never sequenced. It would be important to sequence the other band and ensure that it is HGF. Please clarify.

2) The authors argue that nucleolin localizes to the cell surface, but no data is presented to support this idea. The authors should clarify this point to indicate that since others have previously shown that nucleolin can be localized to the cell surface and since the current study suggests that HGF and nucleolin interact that perhaps nucleolin is a binding partner for HGF.
3) The cell spreading data is expressed as percent of control. It may be easier to interpret if it is expressed as percentage cell spreading. It’s not clear from the materials and methods how cell spreading is assessed.

4) The source of the prostatic stromal cells should be stated in the materials and methods.

5) Figure 2a: What matrix were the cells grown on?

6) Figure 6a, 6b and 6c: Bands are difficult to visualize which makes it hard to evaluate the data.

Discretionary Revisions (which the author can choose to ignore)

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

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

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.