Reviewer’s report

Title: Integrative genome-wide expression profiling identifies three distinct molecular subgroups of renal cell carcinoma with different patient outcome

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Reviewer: Masatsugu Moriyama

Reviewer’s report:

The authors integrated gene expression data from 97 primary renal cell carcinomas (RCCs), 15 metastasis and 34 cell lines using the PANTHER Classification System. They found that RCCs and cancer cell lines were subdivided into 4 groups by gene expression patterns composed of 4 dominant pathways. Three out of the 4 groups, named A, B and C, showed distinct prognosis and tumor vascularity, but they were not correlated with histologic features. Based on their data, they concluded that newly identified genome-wide signature may exhibit common molecular mechanisms characteristic for the biology of RCC.

Major Compulsory Revisions

1. Authors described that the expression profiles were independent of their histological features. However, most of the papillary RCC cases were subdivided in group C. It is clear that papillary RCC tends to be restricted to group C. Therefore, authors should explain the inconsistent description.

2. Authors described that gene expression profiles were not linked to copy number alterations. However, it is not well explained it in the result nor in the discussion section. They should be described more clearly.

3. Authors should describe the influence of the 4 pathways on the prognosis of patients.

4. Authors should describe the molecular functions of DEK and MSH6.

5. Fuhrman nuclear grading system should be used.

6. The sentence “The four “dominating pathways”, “Inflammation”, “Angiogenesis”, “Integrin” and “Wnt” presented by PANTHER, consist of 476, 354, 365 and 497 genes (pathway-related plus downstream targets), respectively.” in the page 11 should be described in the Results section, not the Discussion.

Minor Essential Revision

1. Fig.2B appeared after Fig.2C and 2D in the text.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests.