Reviewer's report

Title: Fibulin-1 is Epigenetically Down-regulated and Associated with Bladder Cancer Recurrence

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Reviewer: Jiaoti Huang

Reviewer's report:

In the manuscript by Xiao et al, the authors studied the function of Fibulin-1, a member of a growing family of extracellular glycoprotein, in bladder cancer. The authors discovered that fibulin-1 was significantly down-regulated in bladder cancer, and its dysregulation was associated with bladder cancer progression and recurrence. The mechanism for downregulation of fibulin-1 was DNA methylation in bladder cancer cell lines and tissues. Overexpression of fibulin-1 significantly suppressed tumor growth, induced tumor cell apoptosis, decreased cell motility, and inhibited angiogenesis in cultured bladder cancer cells and xenograft tumor in nude mice. These results indicate that fibulin-1 is epigenetically down-regulated in bladder cancer, and associated with cancer progression and recurrence. It functions as a tumor suppressor gene and angiogenesis inhibitor in bladder cancer.

This study is somewhat descriptive. However, the authors provide a significant amount of data establishing fibulin-1 as a potential tumor suppressor whose loss appears to be associated with bladder carcinogenesis. The study was well designed, and the experiments well performed with significant findings. I have the following concerns:

1. Major Compulsory Revisions:
   The clinical bladder cancer cases were graded using the old grading system which needs to be corrected. I understand that these are archival cases and at the time of diagnosis and every case was graded using the old system. However, since the new grading system (WHO / ISUP classification 2004) has been popular for years, it is important for the authors to use the new grading system. In general, grade 1 and the lower end of grade 2 tumors are now classified as low grade urothelial carcinoma, while the higher end of grade 2 and grade 3 tumors are classified as high grade urothelial carcinoma.

2. Minor Essential Revisions:
   Although the manuscript is well written and easy to read, I still find minor grammatical and style errors throughout the manuscript. The authors are encouraged to read the manuscript carefully and make corrections where necessary, which will improve the quality of the manuscript.

Level of interest: An article of importance in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: Nothing to declare