Author's response to reviews

Title: DNA methylation changes in ovarian cancer are cumulative with disease progression and identify tumor stage.

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Author's response to reviews: see over
14 January 2008

Dear BMC Medical Genomics Editors,

Please find enclosed re-revised manuscript entitled: DNA methylation changes in ovarian cancer are cumulative with disease progression and identify tumor stage. We are submitting our manuscript to the new journal, BMC Medical Genomics, upon the invitation of the editors. This manuscript has been revised to fit the format of BMC Medical Genomics, specifically: methods have been indicated in the abstract, sections of the manuscript have been re-ordered, and a paragraph of competing interests has been added.

The attached manuscript reports our study of CpG methylation changes across the spectrum of ovarian cancer using a CpG island-based microarray. Previous studies have looked at hypomethylation of satellite regions in ovarian cancer and CpG methylation late stage tumors, but no study has examined both gain and loss of CpG methylation with disease progression from normal to late stage cancer. We identified both hyper- and hypo methylation of genomic sequences that were cumulative with disease progression. Interestingly, the hypo-methylation was primary at repetitive sequences, while the hyper-methylation occurred primarily at 5’ promoter-associated CpG islands. In addition, we were able to use the changes in CpG methylation to develop a highly accurate and sensitive classifier for differentiating normal and low malignant potential samples from stage III tumors. Because the changes seen in stage III tumors had already begun in stage I tumors, our results suggest more sensitive and targeted techniques may be able to use our results to for early cancer detection. Finally, we validated the CpG island microarray results by bisulfite sequencing and re-expression with 5'-aza-2’deoxyctydine as well as comparison of our DNA methylation results with another studies’ expression analysis. Our study is the first complete analysis of CpG methylation changes with tumor progression and we believe it will be of interest to the readers of BMC Genomics.

The contact information of four suggested reviewers follows on page 2. Thank you for your consideration.

Respectfully,

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