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Epigenetic regulation of CpG promoter methylation in prostate cancer stem cells

Lesley A. Mathews[1], Elaine M. Hurt[2], Xiaohu Zhang[3], William L. Farrar[4] and Marc Ferrer[1]

[1]National Institutes of Health Center for Translational Therapeutics, Human Genome Research Institute, USA
[2]MedImmune, LLC, Gaithersburg, USA
[3]Cancer Stem Cell Section, Laboratory of Cancer Prevention, SAIC-Frederick Inc., National Cancer Institute at Frederick, USA
[4]Cancer Stem Cell Section, Laboratory of Cancer Prevention, Center for Cancer Research, National Cancer Institute at Frederick, USA

Background: Recently, much attention has been focused on gaining a better understanding of the different populations of cells within a tumor and their contribution to cancer progression. One of the most commonly used methods to isolate a more aggressive sub-population of cells utilizes cell sorting based on expression of certain cell adhesion molecules. A recently established method we developed is to isolate these more aggressive cells based on their properties of increased invasive ability. These more invasive cells have been previously characterized as tumor initiating cells (TICs) that have a stem-like genomic signature and express a number of stem cell genes including *Oct3/4* and *Nanog* and are more tumorigenic compared to their 'non-invasive' counterpart. They also have a profile reminiscent of cells undergoing a classic pattern of epithelial to mesenchymal transition or EMT. Using this model of invasion, we sought to investigate which genes are under epigenetic control in this rare population of cells. Epigenetic modifications, specifically DNA methylation, are key events regulating the process of normal human development. To determine the specific methylation pattern in these invasive prostate cells, and if any developmental genes were being differentially regulated, we analyzed differences in global CpG promoter methylation.

Results: Differentially methylated genes were determined and select genes were chosen for additional analyses. The non-receptor tyrosine kinase BMX and transcription factor SOX1 were found to play a significant role in invasion. Ingenuity pathway analysis revealed the methylated gene list frequently displayed genes from the IL-6/STAT3 pathway. Cells which have decreased levels of the targets BMX and SOX1 also display loss of STAT3 activity. Finally, using Oncomine, it was determined that more aggressive metastatic prostate cancers in humans also have higher levels of both *Stat3* and *Sox1*.

Conclusions: Using this method we can begin to understand which genes are epigenetically regulated in the invasive population compared to the bulk tumor cells. These aggressive sub-populations of cells may be linked to the cancer stem cell hypothesis, making their patterns of epigenetic regulation very attractive for biomarker analysis.

Future Directions: Utilizing qHTS screening available at NCGC, new therapeutics aimed at eradicating highly aggressive tumor cells, either singularly or in combination, will be identified.