ABSTRACT

MOLECULAR DIFFERENCES BETWEEN EPITHELIAL & MESENCHYMAL-LIKE CANCER CELLS AS CANDIDATES FOR THERAPEUTIC TARGETS AND BIOMARKERS FOR PANCREATIC ADENOCARCINOMA

By

Arkadeep Sinha

The standard treatments for pancreatic cancer are frustratingly ineffective for long-term benefit with a 5-year survival rate of approximately only 5%. Surgical removal of the tumor extends survival and chemotherapeutic treatment can reduce the bulk of tumors, but neither method completely eliminates cancer cells or their ability to spread and grow. As a result, disease recurrence is the norm. The failure of surgical removal to obtain complete remission indicates that, by the time a cancerous mass in the pancreas is recognized, some of the cancer cells have already disseminated to other parts of the body and established metastatic sites. Likewise, the failure of drugs to kill all cancer cells suggests that certain cells within the tumor have increased resistance to existing treatments. The cause for the failure of these treatments can thus be traced to a subpopulation of cancer cells within each tumor.

There is evidence showing that the process of epithelial to mesenchymal transition (EMT) gives rise to a more aggressive and chemoresistant subpopulation akin to the above-mentioned subpopulation of cancer cells. So, the over-arching hypothesis of this research is that targeting the EMT-derived mesenchymal-like subpopulation of pancreatic cancer cells will lead to better prognosis. The specific hypotheses tested in this study are 1) Mesenchymal-like cancer cells have distinct genetic alterations and

gene expression features relative to their epithelial-like counterparts; and 2) Presence of increased levels of mesenchymal-like cancer cells in a tumor confers a poor prognosis. To test the first hypothesis, we used Affymetrix microarrays and CGH microarrays to compare gene expression and gene amplification measurements, respectively,

between mesenchymal-like and epithelial-like cancer cells in model systems. We identified major gene expression changes that occur during the process of EMT and identified changes in glycogenes affecting sulfation as well as in genes known to bind sulfated molecules like MRC2. We also identified 20 genes with differential copy numbers between the epithelial and mesenchymal-like cells. A study of 11 primary tissues also supported our findings providing additional candidates to target the mesenchymal-like cancer cells and for use as prognostic biomarkers. To test the second hypothesis, we pursued additional investigations of MRC2. First, we performed functional analysis on MRC2 to determine that it is needed for the migration and invasion of cancer cells, and we studied expression in primary tissue to reveal that it is significantly upregulated in the pancreatic cancer tissues compared to the adjacent non-cancerous tissue. To enable more specific detection of mesenchymal-like cancer cells, we developed a novel system of identifying co-expression of MRC2 and the epithelial marker Epcam. We currently are using this system to test whether an increased presence of co-expressing cells associates with poor prognosis.

These complementary approaches provide a broader molecular understanding of the mesenchymal-like aggressive subpopulation of cancer cells and lay a solid foundation to test the over-arching hypothesis.