OCRFA
Ovarian Cancer
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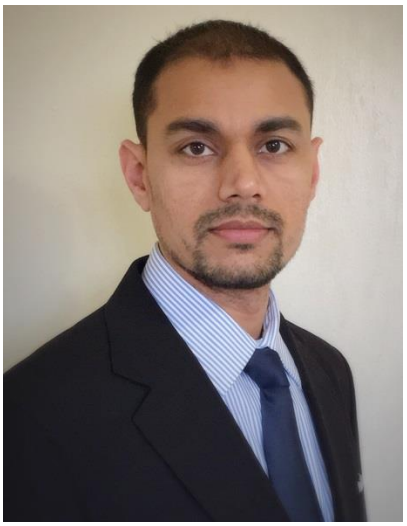
2017 Ann Schreiber Mentored Investigator Award Recipient ($75,000)



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Loss of H2Bub1 Rewires Glutamine Metabolism During Progression of HGSOC

Project Summary

Ovarian cancer is the fifth leading cause of cancer death among women in the United States. There are approximately 22,280 US women diagnosed with ovarian cancer each year and 60% of those cases are diagnosed at an advanced stage, with an overall 5-year survival rate of only 28%. High-grade serous ovarian cancer (HGSOC) is the most common form of ovarian cancer, accounting for over 70% of cases. While standard treatment is initially effective in ovarian cancer, most patients succumb to chemoresistant disease. Therefore, developing effective therapy for HGSOC remains an unmet medical need.

Most human cancers arise due to mutations in DNA. Some mutations can prevent the expression of genes that maintain normal cell growth while others can turn on genes that drive cell growth. Gene expression alterations that do not involve changes to the underlying DNA sequence are referred to as epigenetic changes. Many of these epigenetic changes involve modifications of the histone proteins around which DNA is wound and normally packaged. Aberrant epigenetic changes play a prominent role in many types of cancer, including ovarian cancer. We examined the status of a particular histone modification called H2B monoubiquitylation (abbreviated H2Bub1) in ovarian cancer. We found that the levels of H2Bub1 are reduced or completely lost early in the progression from normal benign cells to ovarian cancer cells. Surprisingly, we found that the loss of H2Bub1 causes changes in the metabolism of the cell in a way that may make them more dependent on an amino acid called glutamine to sustain their uncontrolled growth. In recent decades, it has been shown that cancer cells possess an altered

metabolism that can be a target for therapy. While cancer metabolism has been extensively studied in other cancer types, ovarian cancer metabolism is poorly understood. Here, we propose to characterize and quantify the effects of the depletion of H2Bub1 on the development, progression and metabolism of ovarian cancer. We will quantify the expression levels of genes, proteins and metabolites in cells that have lost H2Bub1 and ask whether these cells are susceptible to drugs that target altered glutamine metabolism. CB-839 is a specific and potent inhibitor of glutamine metabolism, and is the only specific inhibitor of glutamine metabolism that is currently in Phase 1 clinical trials for breast and renal cancer. As a therapeutic approach towards the treatment of ovarian cancer, we will assess the effect of CB-839 in HGSOC as a single agent, as well as in combination with standard chemotherapy drugs. To identify a possible biomarker for the progression of ovarian cancer we will examine the levels of glutamine pathway enzymes in human tissue samples. Quantification of the levels of these enzymes may serve as a potential predictive biomarker to identify patients who will benefit the most from this type of therapy. Our study aims to identify a novel druggable pathway in ovarian cancer that may provide an exciting new therapeutic opportunity for patients that suffer from this disease.

Bio

Dr. Jagmohan Hooda is a postdoctoral fellow in the laboratory of Dr. Ronny Drapkin at Ovarian Cancer Research Center at the University of Pennsylvania in Philadelphia. Dr. Hooda earned his Ph.D. in Cellular and Molecular Biology from The University of Texas at Dallas in 2015. His Ph.D. research focused on understanding the role of heme metabolism in the progression of lung cancer cells. As a result of his graduate work he was awarded a “certificate of recognition for intellectual contribution” by The University of Texas at Dallas. His research article was highlighted as a news report at the University of Texas at Dallas, and featured in a number of newspapers and online blogs. After completing his graduate studies, Dr. Hooda joined Dr. Drapkin’s laboratory to tackle the challenges of ovarian cancer. His studies have focused on early neoplastic events in the fallopian tube that lead to high-grade serous carcinoma. Altered metabolism is a hallmark of cancer. While it is known that tumors display distinct metabolic activities that distinguish them from their benign cellular origins, the metabolic alterations that contribute to the development and progression of ovarian cancer have not been well studied. Dr. Hooda’s studies have identified an unexpected link between a histone epigenetic mark and altered glutamine metabolism. His ongoing work is aimed at defining the impact of this epigenetic mark on cell growth and survival and determining whether targeting glutamine metabolism represents a novel therapeutic opportunity in ovarian cancer.