Hereditary Genetics of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a devastating and prevalent cancer of the liver with high rates of mortality. Major risk factors include chronic viral infection (hepatitis B or C), metabolic syndrome, alcohol use, and exposure to environmental toxins. A positive family history of HCC is an independent risk factor, raising the risk of HCC by more than 2.5-fold. We previously pioneered an investigation into inherited (i.e. germline) genetic factors associated with HCC susceptibility. We completed a pilot analysis of 217 patients with HCC prospectively enrolled from a tertiary medical center for clinical-grade multigene panel genetic testing. We found a surprisingly high rate of pathogenic germline variants in cancer-associated genes in greater than 11% of patients with HCC. This included pathogenic and likely pathogenic variants in genes required for homologous repair, DNA damage response (HR-DDR) including in *BRCA2*, *BRIP1*, *CHEK2*, *FANCA*, *FANCD2*, and *FANCM*. Currently, it is unclear whether defective DNA repair plays a mechanistic role in HCC initiation or progression, or whether such defects increase susceptibility of HCCs to targeted therapy with PARP inhibitors. We hypothesized that inherited loss-of-function variants in specific genes are significantly enriched in patients with HCC, and that carriers can be treated with targeted therapies.

The first aim of this study is to perform a multi-ethnic genetic association study powered to detect clinically meaningful germline variants associated with HCC risk. We have identified over 1500 patients with HCC from various sites in the US, Africa, and South America, and have collected samples from these patients. We have also identified controls from over 200,000 patients without HCC. We are actively performing whole exome sequencing and analysis for patients, as well as performing clinical data abstraction. We will examine rare variants in genes that are associated with the development of HCC, especially candidate genes detected in previous studies. We will also perform an exome-wide analysis to detect new gene associations for HCC. Finally, we will examine whether there are predictors of hereditary cancer syndromes in patients with HCC, including age of onset and family history of cancer.

The second aim is to explore the mechanism of HCC arising from defects in HR-DDR genes and determine the implications for targeted therapy. So far, we have successfully targeted *FANCA* in two cell lines, and *FANCM* in one cell line using CRISPR/Cas9. The cells appear to be more sensitive to PARP inhibition with olaparib, as compared to the parental cell line. Next, we are examining the role of the HR-DDR genes we previously identified in patients, by targeting them using CRISPR/Cas9 in a mouse model of HCC tumorigenesis. Our assay is designed to detect the effect of loss of the HR-DDR genes on tumor formation. We will then determine whether PARP treatment reduces tumor formation in the animal model.

These innovative studies of the hereditary genetics of HCC have the potential to personalize therapies for the subset of patients with hereditary cancer syndromes, which will impact the care of patients with HCC in the US and worldwide.