The 18th Andrew H. Weinberg Symposium - 2014

"Novel clinical applications of cancer genomics"

Report by Ellen O. Weinberg, Ph.D

On June 19, 2014, the 18th Symposium Lecture was held and we welcomed as keynote speaker, Luis Alberto Diaz, Jr., M.D, Associate Professor, Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center and the Ludwig Center for Cancer Genetics and Therapeutics. The title of his lecture was: "Novel clinical applications of cancer genomics."

As of 2014, many cancer genomes from adult and pediatric tumors have been sequenced. Certain tumor types have many mutations, while others have few mutations. Most mutations are point mutations in oncogenes or tumor suppressor genes, resulting in gain of function (i.e ., KRAS) or loss of function (i.e ., APC or p53) respectively. Since most tumors have a greater number of mutations in tumor suppressor genes, Dr. Diaz emphasized the need to learn how to target tumor suppressors.

How can we use cancer genomic information? Dr. Diaz discussed the recent advances in cancer genomics and highlighted four areas in which somatic cancer genome data can be used. These are 1) identification of immune antigens for targeting in immunotherapy; 2) use of genomic information as biomarkers in tumor diagnostics; 3) aiding tumor classification; 4) identification of therapeutic targets or modifiers.

A promising development is the use of immune checkpoint blockade in cancer immunotherapy. Many cancer cells express immunosuppressive ligands that interact with the Programmed Death-1 (PD-1) receptor on T cells to dampen T cell cytotoxic activity against tumor cells. Inhibitors of PD-1 (PD-1 blockade) are currently being evaluated in many cancer types to boost the T cell immune response to cancer cells. Dr. Diaz discussed his ongoing study using the PD-1 blocker, MK-3475 (Pembrolizumab), in patients with microsatellite instability (MSI) tumors as a way to target the hypermutated tumor genotype.

Another exciting use of genomicsomatic cancer gene data is the use of circulating tumor DNA as biomarkers for cancer diagnostics. All cells release cell free DNA (cfDNA) into circulation during normal cell turnover that can be detected in plasma or serum. The levels of cfDNA are dynamic and vary among individuals and conditions. Genomic sequencing of cfDNA has revealed that tumors also release cfDNA, termed circulating

tumor DNA (ctDNA), in high amounts that likely is due to the rapid cellular turnover of cancer cells. Genomic sequencing of cfDNA has consistently shown that ctDNA contains mutations that are very specific for their tumor of origin. Dr. Diaz discussed his ongoing studies using genomic information from ctDNA to understand not only the biology of ctDNA but its usefulness to monitor response to therapy, the development of resistance to therapy, levels of ctDNA in the various stages of cancer and detection of minimal residual disease. The advantage of using ctDNA is that multiple blood draws are more feasible than repeated biopsies and scans.

Dr. Diaz discussed his recent paper that provided insights into the biology of drug resistance using targeted monotherapy (Diaz et al., Nature 2012). He reported their experience using ctDNA in patients with colon cancer treated with targeted therapy with EGRF blockade. These patients did not initially have KRAS mutations and initially responded to targeted therapy, but using repeated serum genomic analysis of ctDNA, KRAS mutations were progressively detected. Diaz, et. al. concluded that mutation-harboring clones were present at low levels prior to initiation of treatment and single targeted therapy inevitably leads to the growth and overgrowth of mutant cells that were present in tiny amounts within the initial tumor.

Another study by Diaz's group sequenced ctDNA in plasma of patients with 14 tumor types. They observed that the number of ctDNA fragments increased with stage of disease in all cases. This study led Diaz et al to hypothesize that early detection of ovarian and endometrial cancers can be achieved using DNA screening of cells within Pap smears. Currently there are no current screening tests for these cancers but they know the mutational background of these types of cancers. From Pap smears, they collected cells in the endocervical fluid and looked for mutations in 46 regions of the DNA for mutations. They found no false positives and detection of 100% of endometrial cancers and 40% of ovarian cancers. Future studies will validate these studies in larger cohorts.

In summary, using cancer genomic sequencing techniques, somatic mutations in tumors can reveal valuable information on the biology of cancer and also be effective biomarkers. The cost of sequencing should continue to come down. Future applications will focus on filling in the gaps in current understanding of the kinetics and dynamics of ctDNA as well as the unmet needs such as application of ctDNA in pediatric cancers, which generally have lower numbers of mutations.

The potential of this information to provide novel therapeutic and prognostic targets for clinical application is great and will likely continue to revolutionize cancer diagnostics, screening and care.