Search Awards

Back to Search Results | Modify Search | New Search

First Functional Analysis of an Inherited SETD2 Mutation Associated with Renal Cell Carcinoma

Principal Investigator: ARNOLD, REBECCA SUSAN
Institution Receiving Award: EMORY UNIVERSITY
Program: KCRP
Proposal Number: KC180068
Award Number: W81XWH-19-1-0859
Funding Mechanism: Concept Award
Partnering Awards:
Award Amount: $114,459.00

View Public Abstract

TECHNICAL ABSTRACT

Cancer is driven by complex mechanisms at the genetic and cellular levels. Biallelic deficiency of SETD2 through inactivating mutations and deletions occur in up to 20% of primary renal cell carcinoma (RCC) tumors, and SETD2 mutations occur in approximately 50% of metastatic clear cell RCC (ccRCC) cases. SETD2, a histone methyltransferase, plays a role in chromatin structure modulation during transcription elongation by trimethylating lysine 36 of histone H3. In addition, it trimethylates alpha-tubulin at lysine 40, which is required for normal mitosis and cytokinesis. Thus, loss of SETD2 uncovers two of the key hallmarks of cancer: alteration to gene expression and genome instability.

While developing a liquid biopsy assay for RCC, we genotyped patients and control subjects and serendipitously observed a novel inherited non-synonymous single nucleotide variant (SNV) in SETD2 that was statistically overrepresented in RCC patients when compared to non-cancer controls and population controls. The functionality and/or causality of this SNV is completely unknown. Our goal is to investigate whether the SNV in question alters the function of SETD2 a key driver of RCC. We will generate a genome-modified variant of Drosophila melanogaster set2, the functional ortholog of hSETD2, using CRISPR/Cas9 technology. Historically, gene discovery in Drosophila models has fundamentally shaped our understanding of human cancer mechanisms. For example, NF1 (Ras pathway); APC, MYC, ARM, and RB (colon cancer, others); and RAS, SCRB, SRC, LGL1/2 (metastasis) were all primarily modeled in Drosophila. Introduction of the hSETD2 SNV into set2 will allow us to determine the effect of this SNV on Set2 function. Investigation of the phenotypic and functional consequence of the human-disease associated hSETD2 SNV in the set2 locus will mechanistically inform how our novel SNV contributes to RCC onset and ccRCC dissemination during metastasis.

The proposal is innovative because it involves the functional investigation of the first-ever inherited nonsynonomous SNV in SETD2 associated with RCC. The work proposed in this application will determine the molecular and cell biological consequences of the mutation; thus, the scientific impact to basic science will be the mutation-function analysis. Additionally, the identification of a single point mutation that predisposes to RCC would have immediate clinical impact in cancer case finding. This could occur in multiple distinct but related clinical scenarios. In the first scenario, any patient that was diagnosed with RCC during current standard medical practice could be tested for the germline mutation. If it was found, screening of all family members for the mutation could be done and those that tested positive could undergo renal imaging to determine whether a renal mass was present. In a second scenario, there could be screening of healthy asymptomatic individuals for the presence of the mutation. Those found to have the mutation could undergo immediate imaging, and potentially additional follow-up imaging at intervals to aid in early detection of disease. This scenario could be modified to test only high-risk groups, such as those with a positive family history. A third scenario involves individuals with known RCC that have undergone curative resection. If these patients were found to harbor the germline mutation, the remaining kidney would remain at increased risk for development of a second tumor compared to patients with purely sporadic disease. These individuals would therefore justify lifelong follow-up and be considered to have high-risk disease regardless of the tumor grade and stage. Finally, RCC disproportionately affects African Americans, and this non-synonymous SNV is also found disproportionately in the African American population. It is therefore possible that some of the racial disparity of the disease could be accounted for by the presence of the mutation and that African Americans may especially benefit from this discovery through screening and case-finding.

Back to Search Results

Note: Documents in Portable Document Format (PDF) require Adobe Acrobat Reader to view, download Adobe Acrobat Reader (http://get.adobe.com/reader/).

CDMRP © 2015

1077 Patchel Street
Fort Detrick, MD 21702-5024

(301) 619-7071

cdmrpwebmaster@webcdmrp.org (mailto:cdmrpwebmaster@webcdmrp.org)

About Us

The CDMRP originated in 1992 via a Congressional appropriation to foster novel approaches to biomedical research in response to the expressed needs of its stakeholders-the American public, the military, and Congress.

 (https://www.facebook.com/TheCDMRP)  (http://twitter.com/CDMRP) 

(https://www.youtube.com/user/CDMRP)  (/rss/funding_opportunities.xml)