Catherine Waters
PhD Candidate

“Insights into Fhit loss-induced tumorigenesis”

July 27, 2015
B040 New James
2:00pm
VITA

1989 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . Born – Greenville, NC

2011 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . B.S. Biology, Elon University

2011-Present. . . . . . . . . . . . . . . . . . . . . . . . . . . BSGP Candidate, The Ohio State University

COMMITTEE MEMBERS

Dr. Kay Huebner, PhD, Advisor

Dr. John McLaughlin, PhD

Dr. Jeffrey Parvin, MD, PhD

Dr. Fen Xia, MD
ABSTRACT

Cancer cells display an elevated rate of genetic mutation at the single nucleotide and chromosome levels, termed genome instability. Genome instability is a facilitating hallmark of cancer in that it raises the probability of generating cancer-promoting mutations. The molecular processes initiating instability in sporadic cancer have not been defined fully. In early cancer cells, genomic alterations are first seen at a few specific chromosome fragile sites. These fragile sites are exquisitely sensitive to agents that stress DNA replication forks. It is thus thought that replicative stress is a major initiator of genome instability in cancer.

Deletion within fragile site FRA3B, which overlaps exons of the FHIT gene, is a frequent and early genetic alteration in precancerous cells, resulting in reduced or lost Fhit protein expression. Loss of Fhit expression occurs in >50% of human cancers, mostly of epithelial origin. Fhit is a tumor suppressor that, following exogenous introduction, leads to apoptosis in cancer cells. Fhit is also a genome caretaker; loss of Fhit protein activity causes replication stress through reduced TK1 expression and increased DNA breaks in normal and cancer cells. Fhit negative cells demonstrate downstream genome instability, including increased point mutations. This damage originates from deregulation of the Fhit-TK1 pathway. The mechanism of positive regulation of TK1 by Fhit is unknown. Here we show, through examination of TK1 mRNA and protein stability in the absence of Fhit, that Fhit regulates TK1 mRNA post transcriptionally by supporting TK1 mRNA translation, likely via hydrolysis of free 5’ mRNA cap dinucleotides.

The cellular processes that can exploit Fhit loss-induced DNA damage and allow increased accumulation of genome alterations and point mutations in Fhit deficient cells and tissues have only recently been examined. APOBEC3B cytidine deaminase activity is another major source of mutation in cancer. But previous studies have shown that the TC context signature of these enzymes is not observed in sizable fractions of cancers with overexpression of APOBEC3B, suggesting that there must be
cooperating factors that contribute to this pattern of mutagenesis. Because of the dependence of APOBEC3B on ssDNA as substrate for mutation, we hypothesized that Fhit loss creates an environment of ongoing DNA damage ripe for APOBEC3B-mediated mutagenesis. Using data from The Cancer Genome Atlas, we show that FHIT-low/APOBEC3B-high expressing lung adenocarcinomas display significantly increased numbers of APOBEC signature mutations. Tumor samples in this cohort with normal FHIT expression do not exhibit APOBEC hypermutation, despite having high APOBEC3B expression. In vitro, silencing Fhit expression elevates APOBEC3B-directed C>T mutations in the TP53 gene. Furthermore, inhibition of Fhit loss-induced DNA damage via thymidine supplementation decreases the TP53 mutation burden in Fhitlow/APOBEC3B-high cells.

We conclude that APOBEC3B overexpression and Fhit-loss induced DNA damage are independent events that, when occurring together, result in a significantly increased frequency of APOBEC-induced mutations that drive cancer progression. Collectively, these findings support a model where deregulation of the Fhit-TK1 pathway initiates genomic instability in early lesions, providing increased availability of unstable ssDNA regions that can be mutated by enzymes, such as APOBEC3B, to promote tumorigenesis.


RECENT PUBLICATIONS


AWARDS AND HONORS

Pelotonia Graduate Student Fellowship: 2014-present
Ohio State College of Medicine, Systems in Integrative Training Program Fellowship: 2012-2014

FUTURE PLANS

Following graduation, I will start a post-doctoral position in the lab of Dr. Reuben Harris at the University of Minnesota, studying APOBEC-mediated mutagenesis in cancer. Long-term I plan to pursue a career in cancer research.