CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180268

Project Title:
Determining the role of polyploidization in liver cancer development

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Most cells (50-80%) in the liver are polyploid, but the functional role of polyploidy is unknown. Polyploid cells and organisms contain more than the two sets of chromosomes that diploids normally have. Polyploidization in the liver normally occurs around the time of weaning, but ploidy is dynamic and can increase after liver surgery [1], fatty liver disease, and other injuries [2]. Despite these associations, the extent to which ploidy influences liver function or cancer risk remains unknown. Some have hypothesized that a high number of chromosome sets within cells is a long-term risk for cancer, while others think that this could be protective against cancer.

To interrogate the function of polyploidy while avoiding irreversible manipulations of important cell cycle genes, we developed multiple mouse models to transiently and potently alter liver ploidy. Premature weaning, in vivo siRNA knockdown of the genes E2f8 or Anln, and genetically engineered models allowed us to toggle between diploid and polyploid states in mice. In preliminary data, we showed that there was no obvious impact of ploidy alterations on liver function, metabolism, or regeneration, but hyperpolyploid mice suppressed and hyperdiploid mice accelerated tumorigenesis in a mutagen induced HCC model.

Here we propose to use these powerful tools to 1) further investigate the impact of ploidy on more clinically relevant HCC models involving chronic inflammation or fatty liver disease, 2) to examine the mechanisms by which polyploidy might be protective against cancer, and 3) to explore whether or not the transient or long-term induction of polyploidy might serve as an effective liver cancer prevention therapy. Our project aims to answer a fundamental mystery in biology and also aims to test therapeutic strategies inspired by this naturally occurring phenomenon. If successful, we will have pre-clinically validated a strategy to prevent the development of HCCs.