CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP170660

Project Title:
Optogenetic Toolkit for Precise Epigenome Editing in Cancer Cells

Award Mechanism:
High Impact/High Risk

Principal Investigator:
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Entity:
Texas A&M University System Health Science Center

Lay Summary:

In cancer cells, one frequently observed abnormal signature is aberrant DNA modifications, which lead to uncontrolled cell growth and survival. DNA is composed of 4 building blocks: A, T, G and C. A fraction of C is modified by a methyl group and become methylcytosine (mC). mC can be further modified by proteins belonging to the TET family, which convert mC to further oxidized species and ultimately remove the methyl group in the genome. The level and distribution of mC are disorganized in cancer cells, but the cause and effect relations between those changes and cancer phenotypes is hard to be established, largely owing to the lack of powerful tools to precisely generate or erase mC.

To meet this critical need, we propose to devise a light-controllable system called iSPIDER (for ight-Inducible Split DNA Epigenome Rewiring tool ) to modify cytosine in the genome by harnessing the power of light. The iSPIDER system will incorporate spatial, temporal, noninvasive and reversible control over abnormal DNA methylation in cancer, and act as GPS and scalpel to locate desired genomic regions and then accurately alter DNA modifications at those regions. We will first design and optimize iSPIDER tools by using protein engineering and molecular biology approaches, with the goal of erasing methyl groups when cells are irradiated by blue light but doing the opposite when illuminated by red light (Aim 1). Because gastric cancer displays the most striking changes in DNA methylation among all cancers, we will next use gastric cancer cells as an ideal model system to test how iSPIDER reshapes cancer phenotypes before and after light stimulation (Aim 2). If successful, the iSPIDER system will become a revolutionary tool to interrogate cancer epigenetics with unprecedented spatiotemporal resolution. It will also lead to paradigm-shift advances in controlling cancer by targeting pro-oncogenic changes in the human epigenome without altering the genetic codes.