

ABSTRACT

Author: Mendonca, Agnes. PhD

Institution: Purdue University

Degree Received: May 2018

Title: Cross-platform probes for the Detection of Epigenetic Modifications in Single Cells

Major Professor: Chongli Yuan

Cancer is one of the single largest causes of mortality in the U.S.A, with 1 in every 3 individuals expected to develop cancer over their lifetimes. The economic burden of cancer drugs is estimated to reach \$173 billion in the next two years. Despite enormous progresses in cancer therapy, the mortality rate remains high due to the clinical challenges imposed by drug resistance in tumor cells. The origin of drug resistance lies in the heterogeneity of tumors on the basis of features such as cellular morphology, metabolism, and mobility. Diversity in the tumor population, and the resulting clonal selection, can eventually confer resistance and lead to the failure of targeted therapy.

Tumor heterogeneity can be ascribed to multiple causes such as genetic mutations, epigenetic changes, and selective pressure from the tumor environment. A large number of techniques, such as next-generation sequencing (NGS), can elucidate the genetic origins of heterogeneity. Limited tools exist to evaluate the epigenetic contributions. Accumulating literature, as well as our own work, suggests that epigenetic modifications, such as DNA methylation and modifications to its associated proteins, have a prominent role in modulating gene activity. Elucidating the role of epigenetic marks on chromatin state and dissecting their phenotypic contributions are thus critically important towards advancing future cancer treatments.

In this work, we started by evaluating the roles of epigenetic modifications on chromatin and their dynamic interactions with epigenetic enzymes. Built upon this fundamental knowledge, novel tools were developed to track and sort cells based on their epigenetic traits individually and combinatorially. Our sorting platform is compatible with high throughput applications and can process 10^5 cells/min. The developed probes can sort heterogeneous cells into sub-populations

based on the variability in their epigenetic background. A more robust picture of the spatial distribution of modifications within the nucleus is provided by using a microscopy- based platform to image the probes within live cells. The novel platforms developed in this work are used to analyze the contributions of epigenetic modifications to tumor heterogeneity in breast cancer cells and reveal the potential contributions of various epigenetic modifications in drug response and tumor progression.