

Bankhead-Coley Cancer Research Program

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Project Title: Genome Plasticity During ES Cell Differentiation to Neural Lineages

Project Summary: Our long-term goal is to understand the relationship of DNA replication to chromosome structure and function and how misregulation of replication leads to cancer. All cells contain the same genetic information (DNA) but package it with proteins into “chromatin” in characteristic ways that define each cell type. Chromatin is dismantled and re-assembled during each round of DNA replication before each cell division, and we have discovered that the sequence in which segments of DNA are replicated and packaged into chromatin changes as embryonic stem cells turn into different cell types. We have developed new methods that will allow us to study the mechanism by which these changes occur, and how they are linked to changes in the expression of genes and the identity of different types of stem cells. Understanding how and why this temporal program for DNA replication changes in different cell types is important to cancer research for the following reasons. First, it is now appreciated that changes in chromatin packaging profoundly influence the progression of cancer and may be as important or more important than genetic changes. In fact, defects in the temporal order of replication are a known prognostic indicator of cancer progression, yet the reasons for this link are completely unclear. Through our studies, we hope to shed light on how replication relates to chromosome functions, allowing us to understand how these defects are related to cancer. Secondly, recent evidence suggests that cancer may derive from stem cells that cannot lose certain properties of their “stemness”—properties that allow them to grow and divide repeatedly, contributing to the progression of cancer. These properties do not appear to be genetic but instead may be determined by the packaging of chromatin. What is promising about this new line of thinking is that, if true, these properties are not hard-wired into the DNA and so should, in principle and with sufficient knowledge, be reversible and hence “curable.” Our studies may shed light on novel properties of stem cells that are determined by chromatin packaging and which properties identify them as particular types of stem cells. Future studies will examine which of these properties are shared between stem cells and cancer cells. This will not only assist in the detection of cancer properties in tissue biopsies (aiding diagnosis) but may reveal which properties would be the most important to reverse in the treatment of the cancer itself.