

Bankhead-Coley Cancer Research Program

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New Investigator (3-year project)*

Project Title: Regulation of Histone Protein Levels by Tumor Suppressor Chk2 and Its Impact on Genomic Stability

Project Summary: Cancer, characterized by uncontrolled cell division, is the second leading cause of death in America; 50 percent of all men and a third of all women will develop cancer at some point. It is believed that damage to DNA (the inherited genetic material in all eukaryotic organisms—including humans) and other factors that cause genomic instability contribute to cancer formation. Genomic instability is characterized by the increased rate of acquisition of alterations in the DNA and is associated with most, if not all human cancers. Our understanding of the underlying causes of genomic instability and cancer is incomplete and would greatly benefit from further research.

DNA is wrapped around positively charged histone proteins to form filaments called chromosomes. Histones help package the DNA to fit it inside the nucleus of each cell and thus regulate processes such as gene expression that require access to the genetic information contained within the DNA. This fundamental regulation of access to the DNA by chromosome structure suggests that all aspects of normal and abnormal human physiology, including diseases such as cancer, are likely to be influenced by the levels of histone proteins that serve as the building blocks of chromosomes. Due to their positive charge, histones can potentially “stick” non-specifically to the negatively charged DNA and adversely affect processes that require access to DNA. Cells can accumulate “excess” histones when DNA synthesis slows down at the end of S-phase or when DNA damage occurs during S-phase. Elevated histone protein levels lead to DNA damage sensitivity and genomic instability in yeast. Hence, improper histone levels and aberrant chromatin structure may contribute to genomic instability and cancer in humans. In order to avoid the harmful effects of excess histone accumulation, cells have evolved mechanisms to tightly regulate their histone protein levels. We have recently demonstrated that the essential DNA damage response protein Rad53 monitors histone protein levels and targets excess histones for degradation in yeast. Rad53 thus contributes to the maintenance of genomic stability independent of its role in the DNA damage response. Tumor suppressor Chk2 is the human counterpart of the yeast Rad53 kinase. Like Rad53, Chk2 has important functions in the DNA damage response pathways including activation of the well-known tumor suppressor p53. Mutations in human Chk2 result in a subset of the inherited cancer predisposition condition known as Li Fraumeni syndrome, which results in a higher frequency of early onset cancers among individuals in affected families. We suspect that Chk2 is involved in the regulation of histone levels in human cells and that this function is important for maintaining genomic stability. Hence, we are applying our findings in yeast to human cells and investigating if Chk2 and the highly related kinase Chk1, as well as their known upstream and downstream factors, are playing a role in regulating histone levels. We will also extend our studies to analyze the effect of inappropriate histone levels on the genomic stability of human cells. Our studies may discover novel mechanisms via which histone/chromatin metabolism and Chk2 prevent genomic instability and cancer.