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“The role of misregulated epigenetic mechanisms in cellular transformation and colorectal carcinoma”

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Genetic mutations are traditionally considered the culprits behind the onset and development of cancer. However, it has become increasingly apparent that alterations in the epigenetic controls of gene expression that include DNA methylation, posttranslational modifications of histones, and microRNAs also contribute significantly to tumorigenesis. While aberrant DNA hypermethylation results in the epigenetic silencing of tumor suppressors in various cancers, the relationship between alterations in histone modifications and the pathogenesis of cancer are significantly less understood. In addition, the combined functions of genetic and epigenetic alterations in promoting tumorigenesis remain unclear, and this continues to be a critical limiting factor in our understanding of the mechanisms that contribute to the pathogenesis of cancer.

The proposed research plan is designed to advance the analysis of mechanisms by which epigenetic and genetic alterations direct gene expression changes that promote human colorectal carcinoma. One key area of the study involves the identification and characterization of epigenetic and gene expression changes in colon cancer that are established by alterations in the H3K4me3 effector protein ING2. We recently identified that alterations in ING2 expression levels in human colon tumors and colon cancer cell lines correlate with significant changes in the global levels of the active histone modification H3K27 acetylation (H3K27ac) and the expression levels of several target genes of the tumor suppressor p53. Consistent with the changes in H3K27ac, a histone mark that is enriched at enhancer regions, we have identified a significant enrichment of ING2 at enhancer elements of several p53 target genes and have shown that ING2 is coordinately expressed and associates with the histone acetyltransferase p300 in colon cancer tissues. Thus, these findings underscore the significance of investigating the role of ING2 in directing epigenetic and gene expression changes in colon carcinoma. We also plan to establish a paradigm for the functional interplay between ING2-dependent epigenetic alterations and mutant p53-dependent transcription in colon cancer.

The hypothesis that we will test in this project is that ING2 misregulation will lead to altered chromatin states that subsequently result in aberrant expression of p53 target genes and the transformation of colorectal carcinoma cells. The aim of our proposed research is to employ both in vitro biochemical experiments and cell-based assays to address the specific goals of this project. **In Aim 1** we propose to identify the functional role of ING2 and associating proteins in establishing alterations in histone H3 acetylation and gene expression profiles that contribute to the pathogenesis of colon cancer. **In Aim 2** we will investigate the molecular mechanisms by which ING2 protein complexes regulate transcription directed by mutant p53. The proposed studies should provide a greater mechanistic understanding of

epigenetic mechanisms in the deregulation of gene expression by mutp53 an issue that will undeniably advance our understanding of human cancer and will ultimately advance the potential for target-based screening approaches, an issue of great significance in light of the recent successes in targeting histone modification effector proteins/readers for developing cancer therapies.