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Functional Significance of P300/CBP in Melanoma Development

This project aims to investigate a potential new drug target in melanoma. The p300/CBP protein is a crucial regulator of gene expression in cells. It belongs to a class of proteins called "histone acetyltransferases", or HATs. The activity of p300 is closely associated with the chromatin, which is a complex of DNA and a group of proteins called histones that DNA strands loop around. P300 catalyzes a reaction called "lysine acetylation" on the histones, which is an important signal for DNA strands to unwind and become accessible. This then allows genes to be converted into proteins. We hypothesize that p300 plays an important role in melanoma development by abnormally enhancing the expression of growth-promoting genes. This process complements and augments the effects of other genetic abnormalities such as DNA damage and mutation. Collectively they may cause cancer.

Using a chemical compound that specifically inhibits the acetylation function of p300, we have demonstrated that this inhibition leads to decreased proliferation of melanoma cells. In addition to melanoma, we also observed a potent inhibitory effect in a subset of non-small cell lung cancers, as well as glioblastomas. Furthermore, we have identified another gene called cyclin A as a potential surrogate marker of p300 activity in tumor cells, for its level of expression decreased in a dose-dependent manner when cells were treated with the compound. Currently we are attempting to identify the specific mechanisms responsible for mediating this growth inhibitory effect, which will help us to better understand why and how p300 contributes to melanoma development. In addition, we are looking at global changes in gene expression patterns using a microarray approach. This allows us to screen the entire human genome for downstream genes regulated by p300, and to identify any signaling pathway (which is a cascade of events that converts a biological, mechanical or chemical signal into a cellular response) that may be altered by p300. By comparing the patterns of gene expression in different stages of melanoma, we will also be able to identify which genes or pathways are important to all stages of melanoma and which ones specifically contributes to any single stage. Potentially this will lead to more therapeutic targets, more drug development against these targets, and more options in melanoma treatment.