JNK Phosphorylation of p53 Results in a p53-p73 Complex to Induce Apoptosis.

**Kristin Bredhold**[1], Amber Klein[1], Lindsey D. Mayo[1]
[1]Department of Pediatrics, Herman B Wells Center for Pediatric Research, [2]Department of Biochemistry and Molecular Biology, Indiana University School of Medicine

Tumor protein p53 is the most commonly mutated tumor suppressor in human cancers. The p53 family consists of three proteins p53, p63, and p73, which are all transcription factors. Mutant p53 functions as a dominant negative through the interaction with either p63 or p73, while wild-type p53 has yet to be shown heterodimerize with these family members. In order to therapeutically target many human cancers, it is critical to understand how p53 functions in cells to bring about apoptosis. In this study, we first verified mutant p53 complexes with p73 in U373 human glioblastoma astrocytoma cells. In addition, we found that mutant p53 was phosphorylated at threonine 81 (T81), a site proximal to the proline rich domain of p53, which is responsible for induction of apoptosis. This led us to examine wild type p53. We treated U87 glioblastoma cells with chemotherapeutics agents and found wild-type p53 to interact with p73. Since T81 was phosphorylated in the mutant, we examined wild type p53 and found that it was also modified. We explored the possibility that phosphorylation at T81 was central to the heterodimerization of p53 and p73. The JNK kinase has been reported to phosphorylate T81 of p53. We found that activation of JNK resulted in p53-p73 interaction, while blockade of JNK prevented binding of p53 with p73. The interaction of phosphorylated T81 of p53 and the resultant p53-p73 complex binds to the apoptotic promoters of *puma* and *bax* and induces gene expression. Thus, our study provides the first evidence that wild-type p53 forms a complex with p73 to induce apoptosis.

Mentor: Lindsey D. Mayo, Department of Pediatrics, Herman B Wells Center for Pediatric Research; Department of Biochemistry and Molecular Biology, Indiana University School of Medicine