HEALTH RESEARCH ABSTRACT SUBMISSIONS #9

Name *	Sara Reed
Email *	sara-francis@uiowa.edu
Educational Level *	PhD Candidate
If Selected Other	
College *	College of Medicine
Department *	Pharmacology
Title of Research *	Mechanisms of p53 Activation by NIAM, Nuclear Interactor of ARF and Mdm2
Other Authors *	Van Tompkins, PhD (UI Department of Pathology); Jussara Hagen, MS (UI Department of Pharmacology); Katie Thies, BS; Diane Cryderman, BS (UI Department of Biochemistry); Lori Wallrath, PhD (UI Department of Biochemistry); and Dawn E. Quelle, PhD (UI Pharmacology Department)
Introduction & Purpose *	Nuclear Interactor of ARF and Mdm2, NIAM, is a novel regulator of the ARF-Mdm2-p53 tumor suppressor pathway. It collaborates with ARF, promotes p53 transcriptional activity, and is negatively regulated by Mdm2-mediated ubiquitination and proteasome degradation. How NIAM activates p53 is not known, however its ability to do so in ARF-null cells reveals it is an ARF-independent process.
Experimental Design *	Biochemical fractionation, immunofluorescence, and immunoprecipitation experiments were performed to elucidate the role of NIAM in p53 activation and DNA repair. A p53 Lys120-acetylation antibody was used for the immunoblotting in U2OS cells overexpressing NIAM.

Results *

Our preliminary data suggest that NIAM could activate p53 by either competing Mdm2 away from p53-Mdm2 complexes and/or by inducing lysine 120 acetylation of p53 via the Tip60 acetyltransferase. p53 acetylation at K120 is known to be regulated by two different histone acetyltransferases, Tip60 and MOF, and to promote the specific upregulation of apoptotic genes by p53. We show that NIAM interacts with Tip60 thru its N-terminal sequences (aa 1-164) and strongly promotes p53 acetylation of K120, suggesting a functional NIAM-Tip60 interaction in vivo. Tip60 is an established chromatin modifying protein that influences chromatin structure and cancer gene expression. Consistent with these characteristics of Tip60, we discovered that NIAM is a chromatin-associated protein that binds to transcriptionally active regions of the genome. Other findings connect Tip60 and NIAM. Tip60 acts through p53, ARF and Myc to control transcription and promote the DNA damage checkpoint response. We found that NIAM, like Tip60, localizes to sites of DNA repair in response to DNA damage and it is already established that the absence of either protein leads to chromosomal instability.

Conclusions *	These compelling observations link NIAM with chromatin regulation and DNA damage repair, potentially via Tip60 signaling, all of which are important for the maintenance of chromosomal stability and prevention of cancer.

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