

# Abstract

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## **NAD<sup>+</sup> modulates p53 DNA binding specificity and function.**

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**BACKGROUND:** DNA damage induces p53 DNA binding activity, which affects tumorigenesis, tumor responses to therapies, and the toxicities of cancer therapies (B. Vogelstein, D. Lane, and A. J. Levine, *Nature* 408:307-310, 2000; K. H. Vousden and X. Lu, *Nat. Rev. Cancer* 2:594-604, 2002). Both transcriptional and transcription-independent activities of p53 contribute to DNA damage-induced cell cycle arrest, apoptosis, and aneuploidy prevention (M. B. Kastan et al., *Cell* 71:587-597, 1992; K. H. Vousden and X. Lu, *Nat. Rev. Cancer* 2:594-604, 2002).

**OBJECTIVE:** Small-molecule manipulation of p53 DNA binding activity has been an elusive goal, but here we show that NAD(+) binds to p53 tetramers, induces a conformational change, and modulates p53 DNA binding specificity in vitro.

**FINDINGS:** Niacinamide (vitamin B(3)) increases the rate of intracellular NAD(+) synthesis, alters radiation-induced p53 DNA binding specificity, and modulates activation of a subset of p53 transcriptional targets.

**CONCLUSION:** These effects are likely due to a direct effect of NAD(+) on p53, as a molecule structurally related to part of NAD(+), TDP, also inhibits p53 DNA binding, and the TDP precursor, thiamine (vitamin B(1)), inhibits intracellular p53 activity. Niacinamide and thiamine affect two p53-regulated cellular responses to ionizing radiation: rereplication and apoptosis. Thus, niacinamide and thiamine form a novel basis for the development of small molecules that affect p53 function in vivo, and these results suggest that changes in cellular energy metabolism may regulate p53.

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