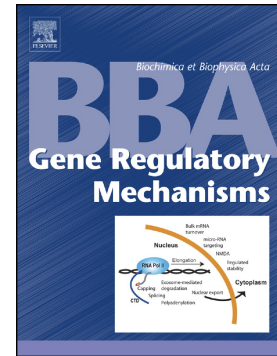


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# HMGB1-mediated DNA bending: distinct roles in increasing p53 binding to DNA and the transactivation of p53-responsive gene promoters

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*Abbreviations:* HMG, high mobility group; WT, wild-type; oxiHMGB1, oxidized HMGB1; HMGB1 $\Delta$ C, HMGB1 lacking the acidic C-terminal tail; EMSA, electrophoresis mobility shift assay.

*Keywords:* HMGB; p53; DNA bending; DNA-protein interaction; promoter transactivation.

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## A B S T R A C T

HMGB1 is a chromatin-associated protein that has been implicated in many important biological processes such as transcription, recombination, DNA repair, and genome stability. These functions include the enhancement of binding of a number of transcription factors, including the tumor suppressor protein p53, to their specific DNA-binding sites. HMGB1 is composed of two highly conserved HMG boxes, linked to an intrinsically disordered acidic C-terminal tail. Previous reports have suggested that the ability of HMGB1 to bend DNA may explain the *in vitro* HMGB1-mediated increase in sequence-specific DNA binding by p53. The aim of this study was to reinvestigate the importance of HMGB1-induced DNA bending in relationship to the ability of the protein to promote the specific binding of p53 to short DNA duplexes *in vitro*, and to transactivate two major p53-regulated human genes: *Mdm2* and *p21/WAF1*. Using a number of HMGB1 mutants, we report that the HMGB1-mediated increase in sequence-specific p53 binding to DNA duplexes *in vitro* depends very little on HMGB1-mediated DNA bending. The presence of the acidic C-terminal tail of HMGB1 and/or the oxidation of the protein can reduce the HMGB1-mediated p53 binding. Interestingly, the induction of transactivation of p53-responsive gene promoters by HMGB1 requires both the ability of the protein to bend DNA and the acidic C-terminal tail, and is *promoter-specific*. We propose that the efficient transactivation of p53-responsive gene promoters by HMGB1 depends on complex events, rather than solely on the promotion of p53 binding to its DNA cognate sites.

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