

## High mobility group protein-mediated transcription requires DNA damage marker $\gamma$ -H2AX

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### Abstract

© 2015 IBCB, SIBS, CAS. All rights reserved. The eukaryotic genome is organized into chromatin, the physiological template for DNA-dependent processes including replication, recombination, repair, and transcription. Chromatin-mediated transcription regulation involves DNA methylation, chromatin remodeling, and histone modifications. However, chromatin also contains non-histone chromatin-associated proteins, of which the high-mobility group (HMG) proteins are the most abundant. Although it is known that HMG proteins induce structural changes of chromatin, the processes underlying transcription regulation by HMG proteins are poorly understood. Here we decipher the molecular mechanism of transcription regulation mediated by the HMG AT-hook 2 protein (HMGA2). We combined proteomic, ChIP-seq, and transcriptome data to show that HMGA2-induced transcription requires phosphorylation of the histone variant H2AX at S139 (H2AXS139ph;  $\gamma$ -H2AX) mediated by the protein kinase ataxia telangiectasia mutated (ATM). Furthermore, we demonstrate the biological relevance of this mechanism within the context of TGF $\beta$ 1 signaling. The interplay between HMGA2, ATM, and H2AX is a novel mechanism of transcription initiation. Our results link H2AXS139ph to transcription, assigning a new function for this DNA damage marker. Controlled chromatin opening during transcription may involve intermediates with DNA breaks that may require mechanisms that ensure the integrity of the genome.

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### Keywords

ATM, Chromatin-associated proteins, DNA damage, Gata6, HMGA2, TGF $\beta$ 1, Transcription,  $\gamma$ -H2AX