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Arsenic induces the highly carcinogenic polyadenylation of canonical histone mRNA by downregulating stem-loop binding protein

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The replication-dependent histone genes are the only metazoan genes whose messenger RNA (mRNA) does not terminate with a poly(A) tail at the 3' end. Instead, the histone mRNAs display a stem-loop structure at their 3' end. Stem-loop binding protein (SLBP) binds the stem-loop and regulates canonical histone mRNA metabolism. We report that exposure to arsenic, a carcinogenic metal, decreases cellular levels of SLBP by inducing its proteasomal degradation and inhibiting SLBP transcription via epigenetic mechanisms. Notably, arsenic exposure dramatically increases polyadenylation of canonical histone H3.1 mRNA possibly through downregulation of SLBP expression. The polyadenylated H3.1 mRNA induced by arsenic is not susceptible to normal degradation that occurs at the end of S phase, resulting in continued presence into mitosis, increased total H3.1 mRNA, and increased H3 protein levels. Excess expression of canonical histones has been shown to increase sensitivity to DNA damage, as well as increase the frequency of missing chromosomes and induce genomic instability. Our hypothesis is that H3.1 genes are initially transcribed with a normal stem-loop construct at the 3' end of the mRNA. Arsenic depletes nuclear levels of SLBP resulting in H3.1 transcripts unbound to SLBP. These unbound transcripts lose their stem-loop structure at the 3' end and acquire a poly(A) tail, which increases the half-life and facilitates translation of the mRNA, two factors that provide for increased H3.1 protein levels. The poly(A) H3.1 mRNA is not susceptible to normal degradation that occurs at the end of S phase allowing for its presence in other phases of the cell cycle. Over-expression of SLBP suppressed the effect of As on H3.1 polyadenylation. Knockdown of SLBP by siRNA induced anchorage independent growth of BEAS2B cells. Transfection of Polyadenlated H3.1 but not H3.3 also induced anchorage independent growth in BEAS2B cells. Anchorage independent growth was also induced in human Urothelial cells by transfection of polyadenylated H3.1 but not H3.3.

Biography

Hong Sun is presently working as an Assistant Professor, Department of Environmental Medicine at the New York University School of Medicine, USA.

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