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LncRNA UCA1 Antagonizes Arsenic-Induced Cell Cycle Arrest through Destabilizing EZH2 and Facilitating NFATc2 Expression

Arsenic (As) is a widespread metalloid contaminant, and its internal exposure is demonstrated to cause serious detrimental health problems. Albeit considerable studies are performed to interrogate the molecular mechanisms responsible for As-induced toxicities, the exact mechanisms are not fully understood yet, especially at the epigenetic regulation level. In the present study, it is identified that long non-coding RNA (lncRNA) urothelial cancer associated 1 (UCA1) alleviates As-induced G2/M phase arrest in human liver cells. Intensive mechanistic investigations illustrate that UCA1 interacts with enhancer of zeste homolog 2 (EZH2) and accelerates the latter’ s protein turnover rate under normal and As-exposure conditions. The phosphorylation of EZH2 at the Thr-487 site by cyclin dependent kinase 1 (CDK1) is responsible for As-induced EZH2 protein degradation, and UCA1 enhances this process through increasing the interaction between CDK1 and EZH2. As a consequence, the cell cycle regulator nuclear factor of activated T cells 2 (NFATc2), a downstream target of EZH2, is upregulated to resist As-blocked cell cycle progress and cytotoxicity. This current study unearths a novel prosurvival signaling pathway conducted by EZH2 under As-induced cell cycle arrest. In conclusion, Our present study obtains novel insights into the complex networks of defense mechanisms against As threat, and opens a new path to understand the deregulation of cell cycle progression under pollutant exposure. The findings decipher a novel prosurvival signaling pathway underlying As toxicity from the perspective of epigenetic regulation: UCA1 facilitates the ubiquitination of EZH2 to upregulate NFATc2 and further antagonizes As-induced cell cycle arrest.

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