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Roles of oxidative stress and the ERK1/2, PTEN and p70S6K signaling pathways in arsenite-induced autophagy

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HIGHLIGHTS

- Arsenite reduced OGG1 and increased expression of 8-OHdG and ATF3 in uroepithelial cells.
- Arsenite-induced autophagy was suppressed by reactive oxygen species (ROS) scavenger in human uroepithelial cells.
- Arsenite-induced autophagy is regulates by the PTEN, p70S6K and ERK1/2 signaling pathways.

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ABSTRACT

Studies show that arsenite induces oxidative stress and modifies cellular function *via* phosphorylation of proteins and inhibition of DNA repair enzymes. Autophagy, which has multiple physiological and pathological roles in cellular function, is initiated by oxidative stress and is regulated by the signaling pathways of phosphatidylinositol 3-phosphate kinase (PI3K)/mammalian target of rapamycin (mTOR)/p70S6 kinase (p70S6K) and extracellular signaling-regulated protein kinase 1/2 (ERK1/2) that play important roles in oncogenesis. However, the effects of arsenite-induced oxidative stress on autophagy and on expression of related proteins are not fully understood. This study found that cells treated with sodium arsenite had reduced 8-oxoguanine DNA glycosylase 1 (OGG1) and increased 8-hydroxy-2′-deoxyguanosine (8-OHdG) and activating transcription factor (ATF) 3 in SV-40 immortalized human uroepithelial (SV-HUC-1) cells. Arsenite also increased the number of autophagosomes and increased levels of the autophagy markers Beclin-1 and microtubule-associated protein 1 light chain 3B. Reactive oxygen species scavenger decreased arsenite-induced autophagy in SV-HUC-1 cells. Our previous work showed that arsenite induced phosphorylation of the ERK1/2 signaling pathway. The current study further showed that arsenite decreased phosphatase and tensin homologue (PTEN) levels and increased phospho-p70S6 kinase (p-p70S6K) in SV-HUC-1 cells. However, both kinase inhibitor U0126 and the DNA (cytosine-5-)-methyltransferase 1 (DNMT1) inhibitor 5-aza-deoxycytidine abolished the effect of arsenite on expressions of PTEN and p-p70S6K. These results show that autophagy induced by arsenite exposure is mediated by oxidative stress, which regulates activation of the PTEN, p70S6K and ERK1/2 signaling pathways. Thus, this study clarifies the role of autophagy in arsenite-induced urothelial carcinogenesis.

1. Introduction

Epidemiological studies indicate that arsenic exposure is associated with increased risk of several cancers, including cancers of the lung, skin and bladder (Chen and Wang, 1990). Through various mechanisms, arsenic generates reactive oxygen species

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