an increased epidermal thickness and an increased fraction of epidermal cells expressing proliferating cell nuclear antigen (PCNA) in mice exposed to arsenite compared with control mice. In mice exposed to arsenite plus UVR there was a synergistic effect on proliferation. However, the increased proliferation was already apparent at the lowest arsenite dose used (1.25 mg/l) and did not increase at higher doses. These results are consistent with the hypothesis that arsenite acts as a cocarcinogen with a second (genotoxic) agent by inhibiting DNA repair and increasing proliferation. In addition, our data suggests that arsenite-induced increases in epithelial cell proliferation might be a necessary, but not a sufficient, cause of cocarcinogenisis with UVR, since increased proliferation alone does not lead to skin cancer and does not correlate with cocarcinogenesis. This work was supported by NIEHS grant ES09252 and is part of Center programs supported by Grants ES00260 from NIEHS and CA16087 from NCI.

Arsenic-Induced Mitogenic Cell Signaling Pathways

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Environmental or occupational exposure to arsenic is associated with a greatly increased risk of skin, urinary bladder and respiratory tract cancers in arseniasis-endemic areas throughout the world. We have employed in vitro and in vivo models to examine the effects of arsenic on the urinary bladder epithelium. Mice exposed to 0.01 percent sodium arsenite in the drinking water demonstrated marked hyperproliferation of the bladder uroepithelium within 4 weeks after initiating treatment. The response was accompanied with accumulation of arsenic and induction of activating protein-1 (AP-1) in the urinary bladder tissue . Furthermore, arsenic induced activation of major mitogenic mediators, such as epidermal growth factor receptor (EGFR) and extracellular signal-regulated protein kinase (ERK), in the uropeithelium. This response is also accompanied with increased levels of non-receptor tyrosine kinase c-Src interacting with the EGFR. Consistent with these in vivo observations, arsenic activates c-Src in a human uroepithelial cell line. Using pharmacological and genetic inhibition of Src, we found that c-Src activity is a prerequisite for EGFR and ERK activation in these cells. In conclusion, arsenic shares many properties of tumor promoters by affecting specific cell signal transduction pathways responsible for cell proliferation of initiated cells or increasing the mutational rate.

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ABSTRACTS

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