ROLE OF MITOCHONDRIAL TRANSCRIPTION FACTOR A (MTTFA) IN ARSENIC-INDUCED CELL PROLIFERATION AND DNA DAMAGE IN HUMAN PROSTATE EPITHELIAL CELLS

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Abstract: Prostate cancer is the second leading cause of cancer death in American men. Increasing number of evidences from both epidemiological and experimental studies has shown a significant association between prostate cancer and chronic exposure to inorganic arsenic. Further evidence for the association between arsenic exposure and prostate cancer comes from a report of elevated level of Prostate cancer mortality in a population from certain parts of US that was exposed to higher level of arsenic through drinking water. However, the mechanism for arsenic-induced prostate cancer is not well understood. Mitochondria are a major source of oxygen-derived free radicals, also collectively known as reactive oxygen species (ROS). Increased production of ROS and the resultant damage to both mtDNA and nuclear DNA have long been thought to play a key role in carcinogenesis. Mitochondrial aberrations have been identified in cancer of the prostate, bladder, breast, colon, head and neck, kidney, liver, lung, stomach and in the hematologic malignancies, leukemia and lymphoma. Moreover, ROS function in both initiation and promotion of carcinogenesis. Involvement of mitochondria in arsenic-induced DNA damage and -carcinogenesis has also been reported. However, the precise mechanism for the involvement of mitochondria in mediating the adverse effects of arsenic in prostate cancer development is not clear. Nuclear-encoded mitochondrial transcription factor A (mtTFA) controls transcription of the mitochondrial genome. Therefore, the objective of this study was to determine whether arsenic-induced DNA damage and cell proliferation is mediated by mitochondrial transcription factors mtTFA. The prostate epithelial cells, RWPE-1, were given acute and/or chronic treatment of various concentrations of arsenic. The effect of arsenic on cell proliferation was measured by cell counts and the DNA damage was measured by comet assay. Arsenic-induced gene expression changes were measured by quantitative real-time PCR and/or western blot analysis. The result of this study revealed increased proliferation and DNA damage of RWPE-1 cells exposed to arsenic. Sequencing of mt-DNA revealed several point mutations in mitochondrial genome. A pattern of dose-dependent increase in mtTFA expression by acute exposure to arsenic was observed. The increased expression of mtTFA may result in increased mitochondrial ROS and ROS-induced oxidative DNA damage. In summary, this study provides a mechanistic evidence for the involvement of mitochondria in arsenic-induced DNA damage and potentially in arsenic-induced carcinogenesis in human prostate epithelial cells. The findings of this study suggest that mtTFA could be targeted to inhibit the growth of prostate cancer.