EPIGENETIC BASIS FOR ARSENIC- AND ESTROGEN-INDUCED CELL PROLIFERATION AND DNA DAMAGE

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Abstract: Prolonged exposure to arsenic and estrogen causes human cancers in target organs. Both arsenic and estrogen have been shown to induce cell proliferation and DNA damage that are associated with neoplastic transformation in cells of target organs. However, the molecular mechanism for arsenic and estrogen-induced cell proliferation and DNA damage is not well understood. Recent evidences suggest that epigenetic changes of DNA methylation and histone modifications are involved in the regulation of several classes of genes including cell cycle and DNA repair genes. Therefore, the objectives of this study were to test whether arsenic- and estrogen-induced cell growth and DNA damage is associated with alterations in the epigenetic machinery. The target organ cells (human breast and prostate epithelial cells) were exposed to either estrogen or arsenic as well as in combination of these two chemicals. The cell growth was measured cell count analysis and was further confirmed at molecular level by analysis of cell cycle genes expression. DNA damage was measured by DNA fingerprinting and comet assay. The expression of DNA repair genes was also quantified by real-time PCR. The expression of the genes involved in epigenetic regulations (DNA methylation and histone modifications) was measured by real-time PCR and/or western blot analysis. The result of this study revealed that both arsenic and estrogen exposures causes increased cell proliferation and DNA damage. The aberrant expression of several genes involved in epigenetic process was also observed in this study. Therefore, the findings of this study suggest that arsenic and estrogen induces cell growth and DNA damage, at least in part, by epigenetic regulation of cell cycle and DNA repair genes.