OXIDATIVE STRESS AND EPIGENETIC SUSCEPTIBILITY TO KIDNEY CANCER

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Abstract: Decreased antioxidant function during aging and increased production of reactive oxygen species from endogenous sources and exogenous factors, such as environmental toxicants, leads to increased burden of oxidative stress in human. Chemicals-induced oxidative stress has been implicated in cancer development. The carcinogenic chemicals exert adverse effects through multiple mechanisms, and therefore the role of oxidative stress alone in cancer development is confounded by other mechanism activated in parallel by the chemicals. Kidney is one among the many target organs for oxidative stress-induced adverse effects including cancer development. Whether the chronic oxidative stress alone is sufficient to induce malignant transformation in human kidney cells is not clear. Therefore, the objective of this study was to evaluate the effect of H$_2$O$_2$-induced chronic oxidative stress alone on growth, and malignant transformation in kidney cells. HK-2, a nontumorigenic cell line derived normal human kidney epithelium was exposed to H$_2$O$_2$ for 6 months and its effects on increased growth and neoplastic transformation were evaluated by various cellular and molecular methods. Results of this study revealed that chronic exposure to relatively lower levels of oxidative stress produced by non-cytotoxic concentration of H$_2$O$_2$ caused malignant transformation in normal kidney epithelial cells. This was confirmed by gene expression changes, cell cycle analysis, anchorage independent growth assay and in vivo tumorigenicity in nude mice. Acquisition of stem cell characteristic and EMT phenotype further provides the mechanistic basis for oxidative stress-induced malignant transformation in these cells. Treatment with DNA demethylating agent resulted in decreased growth of HK-2 cells transformed by oxidative stress. In summary, this study for the first time suggests that chronic exposure to elevated levels of oxidative stress alone is sufficient to induce malignant transformation in kidney epithelial cells potentially through acquisition of stem cell characteristics. Additionally, the epigenetic changes-induced by oxidative stress play crucial role in malignant transformation.

Key words: Oxidative Stress, Kidney Cancer, DNA methylation, Histone modification, Epigenetics