N-Acetylcysteine Inhibits Low Dose CT-Induced Increases in Murine Lung Tumorigenesis


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Data from the National Lung Screening Trial (NLST) have suggested that annual computed tomography (CT) screening of at-risk patients can decrease lung cancer mortality by 20%. Concerns remain regarding the long term effects of radiation exposure to the damaged lung cells of heavy smokers and ex-smokers. We previously reported that exposure of transgenic mice expressing a mutant $\text{Ki-ras}^{G12C}$ gene to multiple whole-body CT doses approximating the NLST screening protocol had a significant ($p=0.01$) 43% increase in tumor multiplicity. Using Affymetrix gene chip expression profiling followed by gene ontology analysis, we identified clusters of genes under the categories “immune response” and “oxidative phosphorylation” that were significantly up- and down-regulated, respectively, in mutant Ki-ras expressing mice 10 min after exposure to a single 50 mGy dose of CT radiation compared to controls. We now confirm these findings in mice treated at 8 weeks of age with 4-(methylnitrosoamo)ino)-1-(3-pyridyl)-1-butanone (NNK) followed one week later by 4 weekly doses of 0, 10, 30, or 50 mGy of whole-body CT radiation. Eight months after the last fraction of radiation, mice treated with NNK and exposed to radiation exhibited significant 1.5 to 2-fold increases in radiation-induced tumors compared to mice treated with NNK alone. Treatment of female mice with 0.7% N-acetylcysteine in the diet starting 3 days prior to the first CT exposure and continuing for a total of 5 weeks inhibited the CT-induced increases in lung tumor multiplicity back to levels seen in NNK treated, unirradiated mice ($p<0.03$; one tailed $t$-test). Our data indicate that: 1) exposure to CT radiation in sensitive populations increases the risk of tumorigenesis, 2) this effect may be mediated through immune response and oxidative stress mechanisms, and 3) pre-treatment with an antioxidant may prevent the long term carcinogenic effects of low dose radiation exposure. (Supported by NIH grant CA136910)