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Nrf2-activated Expression of Sulfiredoxin Contributes to Urethane-induced Lung Tumorigenesis

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Abstract

Lung cancer is the leading cause of cancer death worldwide. Cigarette smoking and exposure to chemical carcinogens are among the risk factors of lung tumorigenesis. In this study, we found that cigarette smoke condensate and urethane significantly stimulated the expression of sulfiredoxin (Srx) at the transcript and protein levels in cultured normal lung epithelial cells, and such stimulation was mediated through the activation of nuclear related factor 2 (Nrf2). To study the role of Srx in lung cancer development *in vivo*, mice with Srx wildtype, heterozygous or knockout genotype were subjected to the same protocol of urethane treatment to induce lung tumors. By comparing tumor multiplicity and volume between groups of mice with different genotype, we found that Srx knockout mice had a significantly lower number and smaller size of lung tumors. Mechanistically, we demonstrated that loss of Srx led to a decrease of tumor cell proliferation as well as an increase of tumor cell apoptosis. These data suggest that Srx may have an oncogenic role that contributes to the development of lung cancer in smokers or urethane-exposed human subjects.