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Thioredoxin Overexpression Modulates Remodeling Factors in Stress Responses to Cigarette Smoke

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Cigarette smoke (CS) generates reactive oxygen species (ROS) to produce oxidative damage of bronchial epithelial cells. Prolonged repair responses lead to airway remodeling and irreversible airflow limitation. Thioredoxin (TRX) is a redox protein that scavenges ROS to prevent oxidative stress. The aim of this study was to investigate the mechanisms underlying TRX-mediated CS-induced stress relevant to airway remodeling. Results showed that CS stimulated ROS generation and apoptosis in normal human bronchial epithelial (BEAS-2B) cells, and interfered with gene expression of remodeling factors, such as activation of transforming growth factor (TGF)-β1, epidermal growth factor receptor (EGFR), and cyclin-dependent kinase inhibitor (p21), but repressed matrix metalloproteinases (MMP)-9. In particular, TRX-overexpressing bronchial epithelial (TRX-TD) cells reduced CS-induced apoptosis, and suppressed airway remodeling through attenuation of TGF-β1, EGFR, and p21 and upregulation of MMP-9 expression. TGF-β1 was shown to regulate MMP-9 as evidenced by suppression of MMP-9 protein induction by TGF-β1 antibody. In addition, CS produced apoptosis of BEAS-2B cells via TRX oxidation, which activated signal transduction factors, including apoptosis signal-regulating kinase (ASK) 1 and c-Jun N-terminal kinase (JNK). In contrast, TRX-TD cells exposed to CS retained reduced-form TRX, and inactivated ASK1 and JNK to attenuate apoptosis. This study indicated TRX overexpression was involved in CS-induced apoptosis and prevented airway remodeling through ASK1-JNK inactivation and MMP-9 augmentation.

In biological organisms, oxidation-reduction (redox) reactions occur dynamically during metabolism. However, imbalance of redox reaction produces oxidative stress and results in cell injury, inflammation, and tissue damage. Cigarette smoke (CS) is one of the major external sources of reactive oxygen species (ROS) relevant to human lung diseases. Because of the multiple compounds and complexes in CS (Hoffmann & Hoffmann, 1997), tobacco smoking may produce lung inflammation (Hellermann et al., 2002), chronic obstructive pulmonary diseases (Wald & Hackshaw, 1996), and even lung cancer (Hecht, 2003).

Airway epithelium provides a protective barrier against external environments. Several in vitro studies demonstrated CS extract induces oxidative stress and results in apoptosis or necrosis (Banzet et al., 1999; Carnevali et al., 2003). Damaged epithelial cells may prolong the period of epithelial repair and express remodeling mediators, such as growth factors and matrix metalloproteinases (MMP) that contribute to structural changes in bronchial epithelium (i.e., airway remodeling) (Hamilton et al., 2003). This remodeling produces irreversible airflow limitation and increased airway hyperresponsiveness (James et al., 1989). Gene expression of several growth factors including transforming growth factor (TGF)-β1, epidermal growth factor receptor (EGFR), and cyclin-dependent kinase inhibitor (p21) are increased in inflammatory responses. MMP induce digestion of basement membranes to prevent airway inflammation (Yoon et al., 2007) and tumor progression (Martin & Matrisian, 2007).

Thioredoxin (TRX), a known antioxidant with redox active sequence Cys-Gly-Pro-Cys, is ubiquitous in mammals (Hirota et al., 2002; Holmgren, 1985). TRX regulates cellular redox balance, promotes cell growth, inhibits apoptosis, and modulates inflammation (Nakamura et al., 2005; Watson et al., 2004). TRX is presumed to be essential for cell survival, as knockout mice lacking TRX do not survive (Powis & Montfort, 2001; Nonn et al., 2003). Because of the stress-inducible characteristics, TRX is expressed in response to CS, ROS, ionization radiation, and air pollutants (Hirota et al., 2002; Nakamura et al., 1997; Powis & Montfort, 2001). Genetic suppression or inhibition of TRX results in increased ROS generation and apoptosis (Hansen et al., 2006). In TRX transgenic mice there is decreased alveolar

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