Oxidative stresses are believed to play an important role in the induction of both cell adhesion molecules and pro-inflammatory cytokines, a key event in a variety of inflammatory processes. The enzyme heme oxygenase-1 (HO-1) functions as an antioxidant and serves to protect against tissue injury. In this study, we report that HO-1 was induced in cultured human tracheal smooth muscle cells after either treatment with a potent inducer of HO-1 activity, cobalt protoporphyrin IX, or infection with a recombinant adenovirus that carries the human HO-1 gene. Overexpression of HO-1 protected against tumor necrosis factor (TNF)-α-mediated airway inflammation via the down-regulation of oxidative stress, adhesion molecules, and interleukin-6 in both cultured human tracheal smooth muscle cells and the airways of mice. In addition, HO-1 overexpression inhibited TNF-α-induced intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expression, adherence of THP-1 cells, generation of interleukin-6, $p47^{phox}$ translocation, and nuclear factor-κB activation. HO-1 overexpression also attenuated TNF-α-induced oxidative stress, which was abrogated in the presence of both the HO-1 inhibitor, zinc protoporphyrin IX, as well as a carbon monoxide scavenger. In addition, HO-1 overexpression reduced the formation of a TNFR1/c-Src/$p47^{phox}$ complex. These results suggest that HO-1 functions as a suppressor of TNF-α signaling, not only by inhibiting the expression of adhesion molecules and generation of interleukin-6, but also by diminishing intracellular reactive oxygen species production and nuclear factor-κB activation in both cultured human tracheal smooth muscle cells and the airways of mice.