The peroxisome proliferator-activated receptor gamma (PPARγ) plays important roles in the regulation of cellular proliferation, lipid trafficking and glucose metabolism, and PPARγ agonists have been used widely to treat type-II diabetes. However, the effects of the PPARγ activation in the regulation of lung alveolar epithelial cell function remain poorly understood. In this study, we investigated the effects of PPARγ activation on Nox2-derived reactive oxygen species (ROS) production and cell cycle progression in the lungs of middle aged (6-7m old) C57BL/6 wild-type mice (n=10) after intraperitoneal injection of a selective PPARγ agonist (GW1929, 5 mg/kg body weight, daily) for 14 days. Compared to vehicle-treated mice, GW1929 treatment increased significantly the levels of NADPH-dependent ROS production in the lungs as detected by both lucigenin-chemiluminescence using tissue homogenates and DHE fluorescence on lung sections. Furthermore, increased ROS production was accompanied by significant increases in the expressions of Nox2, PCNA and cyclin D1, and the phosphorylation of ERK1/2 and p38MAPK. The in vivo effect of PPARγ activation by GW1929 was further examined by in vitro cell culture. In cultured primary alveolar epithelial cells isolated from mouse lung, GW1929 (5µM for 24 h) increased significantly the NADPH-dependent ROS production and promoted cell cycle progression from G0/G1 into S and G2/M phases, and these effects were abolished by 1) adding a PPARγ antagonist (BADGE, 1µM); 2) knockdown of PPARγ using siRNA; or 3) knockout of Nox2 using siRNA. In conclusion, PPARγ activation induces Nox2-dependent ROS production and the activation of MAPK, PCNA and cyclin D1, which promotes cell cycle progression in the lungs of healthy animals and in cultured normal alveolar epithelial cells.