Emphysema is a major component of Chronic Obstructive Pulmonary Disease (COPD), considering cigarette smoke (CS) as the main risk factor. Currently, treatment of COPD is based on the administration of bronchodilators and corticosteroids to control symptoms and exacerbations, but there is no effective therapies directed to reverse the progression of the disease. Liver growth factor (LGF) is an albumin-bilirubin complex with mitogenic properties, whose therapeutic effects has been previously reported in several rodent models such as injured liver, Parkinson’s disease, testis degeneration, atherosclerosis, heart or hypertension. To address the therapeutic effect of LGF, morphometric and lung function parameters, matrix metalloproteinase (MMP) activity and the expression of several markers such as VEGF, PCNA, 3NT and Nrf2 were assessed in air-exposed and CS-exposed C57BL/6j male mice with and without intraperitoneal injection of LGF administered after long-term cigarette smoke exposure (CSE). CS-exposed mice presented a significant enlargement of alveolar spaces (Lm), higher alveolar internal area (AIA) and loss of lung function that correlated with higher MMP activity, higher expression of 3NT and lower expression of VEGF. CS-exposed mice and then injected with LGF, showed an amelioration of emphysema and improved lung function that correlated with lower MMP activity and 3NT expression, and higher levels of VEGF, PCNA and Nrf2. This study provides evidence that LGF administration produced therapeutic effects once the lung damage was established, postulated as a promising strategy to revert the progression of COPD.