Cancer-associated fibroblasts (CAFs) are important in tumor progression. The autophagy adaptor protein, p62/SQSTM1/Sequestosome-1, is up-regulated in tumors, but down-regulated in CAFs in the early stages of lung adenocarcinoma. We investigated whether p62-induced autophagy might control CAF activation. Under CAF-inducing conditions, like hypoxia or cancer cell co-cultures, p62 ablation or autophagy inhibition with hydroxychloroquine (HCQ) impaired CAF activation and reduced transforming growth factor beta (TGFβ) production, which impeded tumor growth. During CAF activation, p62-induced autophagy up-regulated the expression of the anti-oxidant signaling protein, nuclear factor erythroid 2-related factor 2 (Nrf2), and the ER-stress response regulator, activating transcription factor 6 (ATF6). Genetically or pharmacologically inhibiting the Nrf2-ATF6 pathway totally blocked CAF activation and tumor progression. These results demonstrate that p62 is a key modulator of primary lung adenocarcinoma progression. Thus, targeting the p62-Nrf2 autophagy signaling pathway might be a novel, stroma-focused, cancer prevention and/or treatment strategy.