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Title: Peroxiredoxin 6 attenuates lipopolysaccharide-induced plasminogen activatro inhibitor 1 expression by regulating autophagy

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Body: Objective: To evaluate the roles of Peroxiredoxin(Prdx)6 in the expression of plasminogen activator inhibitor(PAI)-1 in lipopolysaccharide(LPS) induced acute lung injury(ALI). Methods and Results: ALI was induced in Prdx6(-/-) and C57BL/6J mice 4hrs or 24hrs after intratracheal instillation of LPS(5mg/kg), characterized by inflammation in morphology, higher wet/dry ratio, elevated protein concentration and increased neutrophils in bronchial alveolar lavage fluid(BALF), which were more significantly in Prdx6(-/-) mice. After LPS administration, PAI-1 mRNAexpressions were markedly increased in a time-dependant manner and the PAI-1 concentration in BALF were markedly increased at 4hrs and decreased nearly to baseline at 24hrs in Prdx6(-/-) mice compared to C57BL/6J mice. Autophagy was significantly enhenced with higher expression of LC3B in Prdx6(-/-) mice compared to C57BL/6J mice. Primary cultured macrophages were stimulated by LPS (10ug/ml) for 4hrs. The level of reactive oxygen species(ROS) in macrophages from Prdx6 (-/-) mice was significantly higher than that from C57BL/6J mice. The release of PAI-1 was significantly increased in macrophages from Prdx6(-/-) mice compared to wildtype mice after LPS instillation. PAI-1 release was partially suppressed by extracellular signal–regulated kinase(ERK) and p38 mitogen-activated protein kinase inhibitor(MAPK) but not by c-Jun N-terminal kinase inhibitors. Conclusions: In LPS-induced ALI, Prdx6(-/-) mice increased PAI-1 expressions of partially dependent on enhanced autophagy in lungs and p38 MAPK and ERK in macrophages. Thus, Prdx6 possesses anti-fibrinolytic activity under inflammation by regulating autophagy.