Regulation of lung autophagy by proteinase-activated receptor 2 activation

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Regulation of lung autophagy by proteinase-activated receptor 2 activation

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Abstract

Lungs from patients with chronic obstructive pulmonary disease (COPD) display hallmarks of premature ageing, including dysregulated autophagy, leading to cellular senescence. The underlying mechanisms remain unclear. Proteinase activated receptor 2 (PAR2) is a potential therapeutic target for inflammatory conditions, with documented roles in lung pathology. A role for this receptor in lung ageing is yet unexplored.

Autophagic markers LC3 and ATG7 were examined in C57BL/6 wild type and PAR2-/- knock out lung tissue using immunohistochemistry. Autophagic flux was quantified through Marfluorescent imaging (CYTO-ID detection kit) in human bronchial epithelial cell line BEAS-2B and primary human bronchial epithelial cells from healthy (HBEC) and COPD patient donors (DHBEC), after PAR2 stimulation with SLIGKV agonist (cf. VKGILS control).

ATG7 (p<0.005) and LC3 (p<0.05) positive cells were significantly upregulated in PAR2-deficient lungs (Figure 1). PAR2 was present on epithelial cultures, with redistribution upon stimulation. PAR2 stimulation in BEAS-2B resulted in a significant reduction of autophagic vesicles cf. VKGILS (p<0.001). Whilst similar behaviour was observed in HBEC, DHBEC exhibited autophagic flux dysregulation.

This study provides the first data describing a role for PAR2 in the regulation of autophagy in airway epithelia, suggesting a potential mechanism that may underpin premature lung ageing in conditions such as COPD.

Footnotes

COPD - mechanism, Inflammation, COPD
We recommend

Protease activated receptor 2 (PAR2) antagonism reduces pro-inflammatory cytokine production in bronchial epithelial cells
Mariarca Bailo et al., European Respiratory Journal, 2020

Inhibition of IRAK4 suppresses chemokine release from human bronchial epithelial cells
Peter Fenwick et al., European Respiratory Journal, 2013

Downregulation of lysosome-associated membrane protein-2A accelerates cigarette smoke extract-induced aging and apoptosis in human bronchial epithelial cells
Kyoung-Hee Lee et al., European Respiratory Journal, 2019

Role of lamin B1 in COPD pathogenesis
Hiromochi Hara et al., European Respiratory Journal, 2017

Quercetin attenuates inflammation in cigarette smoke stimulated airway epithelial cells: Possible involvement of autophagy
Diandian Li et al., European Respiratory Journal, 2013

S100 Reduction of inflammatory cytokine production in chronic obstructive pulmonary disease (COPD) epithelial cells by protease activated receptor 2 (PAR2) antagonism
M Bailo et al., Thorax, 2019

Prostanoid receptors of the EP4-subtype mediate gene expression changes in human airway epithelial cells with potential anti-inflammatory activity
Radhika Joshi et al., J Pharmacol Exp Ther

Curcumin-induced cell death depends on the level of autophagic flux in A172 and U87MG human glioblastoma cells
Lee et al., Chinese Journal of Natural Medicines, 2020

Therapeutic approaches for COVID-19: Myths and facts
mSystem, 2020

S75 Proteinase activated receptor-2 induced autophagy dysregulation
K McCallum et al., Thorax, 2019