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