European Respiratory Society
Annual Congress 2013

Abstract Number: 5421

Publication Number: P561

Abstract Group: 3.2. Airway Cell Biology and Immunopathology

Keyword 1: COPD - mechanism **Keyword 2:** Infections **Keyword 3:** Respiratory muscle

Title: Resveratrol is superior to dexamethasone in suppressing cytokine release from human airway smooth muscle cells exposed to lipoteichoic acid in COPD

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Body: Lipoteichoic acid (LTA) from gram-positive bacteria induces cytokine expression. This contributes to infection defense, but also increases steroid-resistant airway inflammation in COPD leading to exacerbations. Alternative anti-inflammatory therapies are required, and the plant polyphenol resveratrol (Res) is currently under discussion. Res is an activator of sirtuins, the class III of histone deacetylases (HDACs). Hypothesis: human airway smooth muscle cells (HASMCs) release COPD-related cytokines in response to LTA; Res is superior to the steroid dexamethasone (Dex) in suppressing these cytokines. Ex vivo-cultivated HASMCs of patients with COPD were treated with Res or Dex before stimulation with LTA. CCL2, GM-CSF, IL-6 and IL-8 were analyzed in supernatants by ELISA. Drug effects were investigated in dose-response experiments in the absence and presence of trichostatin A (TSA, blocks class I/II HDACs) and EX527 (blocks the sirtuin SIRT1). In dose-response tests, LTA induced robust releases of CCL2, GM-CSF, IL-6, and IL-8 (each $p<0.05$). Res was superior to Dex in reducing CCL2 (E_{max}: 87% vs. 65% reduction), IL-6 (82% vs. 69%) and IL-8 (52% vs. 8%) in LTA-exposed HASMCs. Both drugs similarly reduced GM-CSF. Res effects were partially reversed by EX527 ($p<0.05$) but not by TSA. Dex effects were partially reversed by TSA ($p<0.05$) but not by EX527. HASMCs contribute to the enhancement of airway inflammation in COPD exacerbations caused by bacterial infections. In HASMCs, Res suppresses cytokine expression via activation of SIRT1, but Dex via class I/II HDACs. Res might be superior to steroids in therapy of exacerbations.