GS01-5 **Type 2 diabetes (T2D) as a comorbidity of COPD - physiology and therapeutics**

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Chronic pulmonary obstructive disease (COPD) is mainly characterized by chronic airway inflammation, mucus plugging and emphysema, leading to death from respiratory dysfunction. Recently, type 2 diabetes (T2D) become known as a comorbidity of COPD, which have a significant impact on prognosis of the COPD patients. Here, we sought to determine i) the molecular mechanisms underlying T2D-related aggravation of COPD phenotypes and ii) the effect of anti-diabetic drug, which is frequently prescribed in the comorbidity, on COPD pathology. First, C57/BL6J- $\beta$ ENaC-Tg mice, a murine model of COPD (Shuto, T., *et al.*, ***Sci Rep.*** **2016**) was subjected to high-fat diet (HFD) feeding and pulmonary phenotypes were analyzed. Comorbidities of COPD and T2D in mice (COPD/T2D mice) showed more severe emphysematous phenotype and pulmonary dysfunction than COPD model mice. Interestingly, our *in vivo* and *in vitro* data showed that pulmonary tissue of COPD/T2D mice have reduced insulin-like factor 1 (IGF1) signals and increased apoptosis-dependent cell death, possible indications of “pulmonary insulin resistance”. Second, we examined the effect of metformin, a clinically available anti-diabetic drug that is known to improve insulin resistance, on COPD pulmonary phenotypes. Administration of metformin (free-drinking water) ameliorated pulmonary emphysema and respiratory function in C57BL/6- $\beta$ ENaC-Tg mice. Thus, we conclude HFD-dependent “pulmonary insulin resistance” as a novel mechanism that complicates COPD under T2D condition and demonstrate the therapeutic potential of metformin for COPD.