6.02 Pharmaceutical Modifications of Human Epididymis Protein 4 (HE4) has Antifibrotic and Anti-Inflammatory Effects on lung fibrosis

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Background: HE4 (human epididymis protein 4), is fibrogenic and increased in fibrotic lung diseases, including systemic sclerosis with interstitial lung disease (SSc-ILD). Hypoxia and inflammation are typical features of SSc-ILD, and hypoxia induces HE4. Dapagliflozin, an inhibitor of sodium-dependent glucose co-transporter 2 (SGLT2) lowers HE4 in renal epithelial cells. We therefore investigated the effect of Dapagliflozin on hypoxia-induced HE4 and on fibrosis and inflammation in an in-vitro model of lung fibrosis.

Methods: Bronchial epithelial cells (16HBE14o-) cultured with Dapagliflozin (0-100μM) were exposed to normoxia (21%O_2) or hypoxia (1%O_2, 6h, 18h normoxia). Lung fibroblasts (CCD-11Lu) were cultured in 10% conditioned medium (CM) from 16HBE14o- cells. HE4, IL-8 and collagen deposition were determined by ELISA and Sirius RED staining.

Results: Dapagliflozin dose-dependently reduced hypoxia-induced HE4 in 16HBE14o- cells (Fig 1). In lung fibroblasts, the hypoxia-CM (Fig 2) showed significantly reduced expression of markers of inflammation (IL-8) and fibrosis (collagen deposition).

Conclusions: HE4 is an important mediator linking fibrosis and inflammation. Dapagliflozin inhibits HE4 and is anti-inflammatory and antifibrotic in a model of lung fibrosis.

Keywords: HE4, interstitial lung disease, lung fibrosis, pharmaceutical modification

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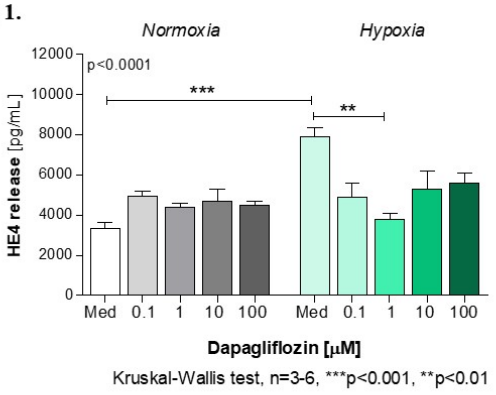
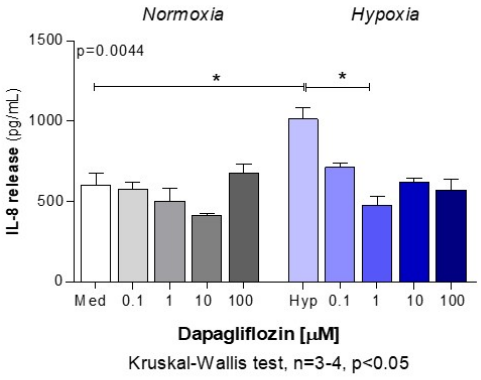
References: (1) Huang X, *et al.* 2022 (doi: 10.1097/FJC.0000000000001268)

Fig 1.

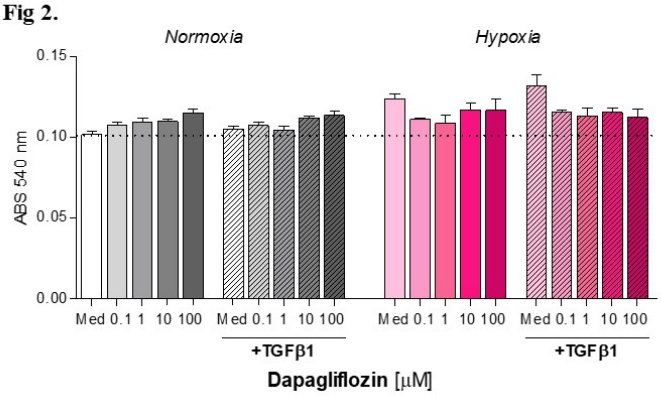


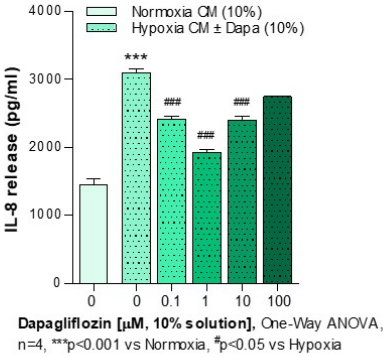
Kruskal-Wallis test, n=3-6, ***p<0.001, **p<0.01



Kruskal-Wallis test, n=3-4, p<0.05

Fig 2.





One-Way ANOVA, n=4, ***p<0.001 vs Normoxia, #p<0.05 vs Hypoxia