Anti-oxidant Gene Expression in Airway Smooth Muscle and Epithelial Cells is Upregulated by Synthetic Secoisolariciresinol Diglucoside (LGM2605)

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Abstract:
Exposure to the air pollutant ozone (O3) worsens pulmonary function and can lead to glucocorticoid insensitivity in asthmatics impairing the possibility of alternative or adjunct treatment approaches. We previously showed that treatment with LGM2605, a synthetic antioxidant (originally derived from flaxseed) prevented O3-induced airway hyperreactivity and decreased inflammatory gene activity in asthmatic mucus macrophages. LGM2605 increased expression of several anti-oxidant genes in the lung tissue of macaques; however, the main cellular target of this compound needed to be clarified.

Methods:
Here we evaluated the effect of LGM2605 on immortalized human airway epithelial cells (HBEC1), obtained from the UC Davis Epithelial Biobank, primary smooth muscle cells (HASM; a generous gift of Dr. Kenyon), and immortalized human alveolar cells (HCAEC; CRL2492). To evaluate the effects of LGM2605, cells were cultured and maintained with 10% fetal bovine serum (FBS) in RPMI media. Cells were exposed to LGM2605 and expression of several anti-oxidant genes in the lung tissue of macaques; however, the main cellular target of this compound needed to be clarified. Expression of TNF, Gata-3, Eotaxin-2, and Sod2 were measured by qPCR.

Results:
SCGM significantly (p<0.05) increased the expression of TNF, Sod2, and Sod2 in HASM but not HBEC1 cells.

Future Direction:
- Increase sample size for dexamethasone treated cells in epithelial cells to further elucidate mechanism of action of dexamethasone in epithelial cells.
- Compare dexamethasone and LGM2605 in HASM cells.
- Evaluate steroid sparing effect if any of LGM2605 in HASM

Summary:
1) LGM2605 did not alter eotaxin2, sod1, or sod2 in A549 cells.
2) In A549 cells without exposure to TBHP, dexamethasone did not alter expression for eotaxin2 and sod2, but did augment sod1 expression in a dose dependent manner.
3) In A549 cells with exposure to TBHP, dexamethasone did decrease eotaxin2 expression and augment sod1 and sod2 expression in a dose dependent manner.

Conclusions:
Airway smooth muscle is highly sensitive to oxidative stress and is amenable to anti-oxidant effects of LGM2605 raising the potential of a novel treatment approach in asthma.

Hypothesis:
LGM2605 promotes antioxidant gene activity in epithelial and smooth muscle cells (A549 and HBEC1, HASM) and decreased inflammatory gene activity when exposed to oxidative stress using TBHP.