Prenatal Environment and Respiratory Disease

The Impact of Chronic Nicotine Exposure on Elastin and TGF-β Signalling

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Background

Prenatal exposure to cigarette smoke increases risk of respiratory disease

- ↑ Risk of asthma[(5)]
- Possible predisposition to COPD (Chronic obstructive pulmonary disease) development[(2)]

Elastin abundance is altered in chronic respiratory disease

- Elastin levels ↑ in severe asthma = disorganization[(4)]
- Elastin levels ↓ in COPD = increased lung compliance[(3)]

The mechanism of altered elastin expression in these diseases is currently unknown

Chronic nicotine exposure decreases baseline elastin expression in lung fibroblasts

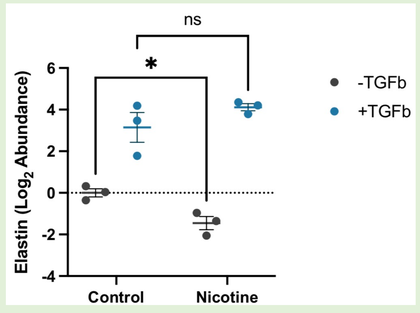


Figure 1: Pilot data indicating that in cells chronically exposed to nicotine, baseline elastin expression is significantly decreased (*=statistically significant; ns=not significant)

TGF-β signalling may be altered by chronic nicotine exposure

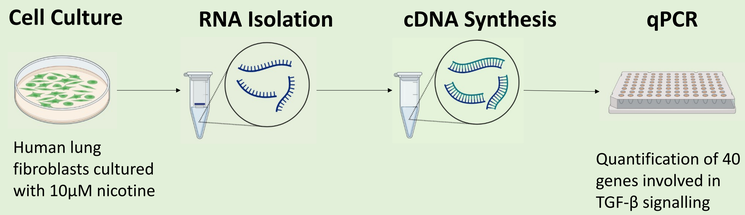
TGF-β (Transforming Growth Factor Beta) is a profibrotic cytokine secreted during inflammation and cell death. TGF-β promotes elastin mRNA stabilization in lung fibroblasts[(1)].

Aim

To determine if chronic nicotine exposure causes alterations to the TGF-β signaling pathway which modulate changes in elastin expression

We hypothesize that chronic nicotine exposure reduces TGF-β signalling by increasing negative regulators of TGF-β

Methods



Statistical Analysis

Genes with the greatest change in abundance are presented as mean fold change (Log2) ± SD, with significance defined as $p<0.05$ (n=3).

Results

Two main genes were altered in expression in the nicotine-treated cells. TGFB1 (Transforming growth factor beta 1) was significantly downregulated (-0.492 ± 0.229, p=0.04*), while MAP2K6 (Mitogen activated protein kinase kinase 6) was upregulated (0.433 ± 0.095, p=0.1).

TGFB1 is the ligand that initiates signalling along the pathway

- ↓TGFB1 = ↓ Elastin

MAP2K6 propagates the signal initiated by TGFB1

- ↑MAP2K6 = ↑ Elastin

Decreased baseline TGF-β signalling in cells chronically exposed to nicotine

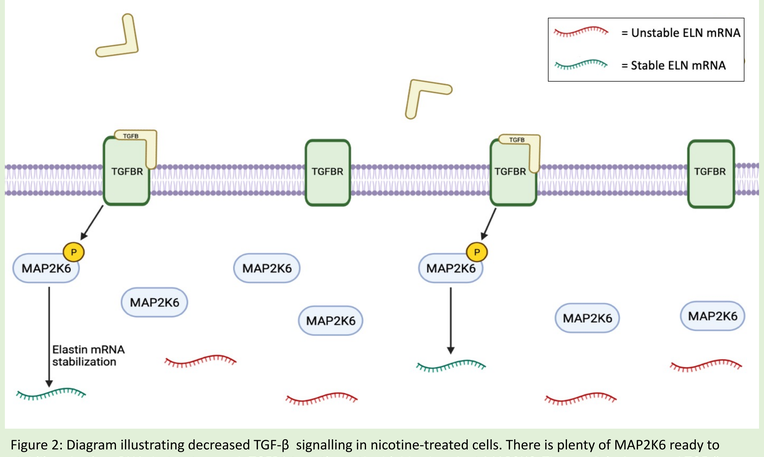


Figure 2: Diagram illustrating decreased TGF-β signalling in nicotine-treated cells. There is plenty of MAP2K6 ready to stabilize elastin mRNA, but not enough TGFB1 to activate the highly abundant MAP2K6. The result is decreased TGF-β signalling at baseline, and decreased ELN mRNA stabilization. (TGFB = Transforming growth factor beta, TGFBR = Transforming growth factor beta receptor, ELN = elastin)

A possible explanation for the elevated MAP2K6 expression is that, in an attempt to compensate for the reduced TGFB1 expression, the cell increases expression of MAP2K6 so that when stimulation with TGF-β does occur the cell is quickly able to stabilize as much elastin mRNA as quickly as possible.

Compensation could become a problem during inflammatory processes as TGF-β is secreted by surrounding cells during inflammation. Since the cell is already primed to stabilize elastin mRNA quickly, too much stabilization may occur via the highly abundant MAP2K6, resulting in increased elastin abundance, which is seen in asthmatic airways.

TGF-β signalling during inflammation in cells chronically exposed to nicotine

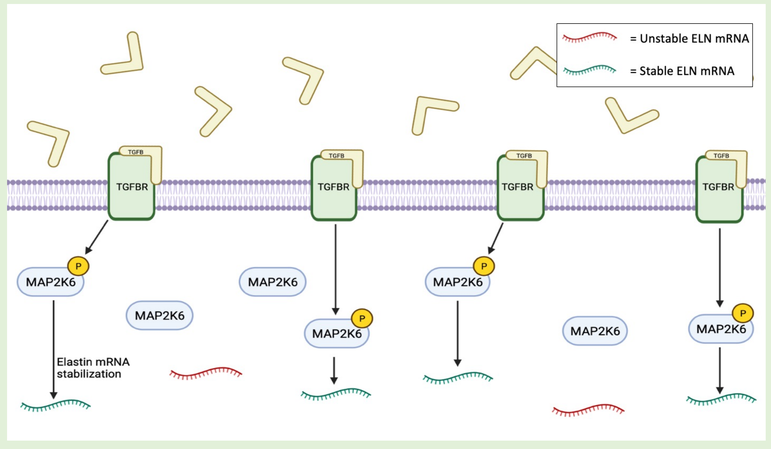


Figure 3: Diagram illustrating increased elastin mRNA stabilization in response to inflammatory stimulation with TGF-β in nicotine-treated cells. Due to increased TGF-β from inflammation, more MAP2K6 is activated and therefore, more elastin mRNA is stabilized. This aligns with airway remodelling seen in asthma.

Conclusion

A decrease in autocrine TGF-β signalling following nicotine exposure may mediate the loss of elastin in human lung fibroblasts. Additionally, increased MAP2K6 abundance, which stabilizes elastin mRNA, may increase elastin mRNA in response to inflammatory stimuli. This could align with airway remodelling seen in asthma.

References

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Diagrams Created with BioRender.com

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