Nutrient modulation of DNA repair in lung cancer
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Background
Lung cancer is the leading cause of cancer death worldwide with 8 million annual global deaths attributed to direct tobacco use, according to a report from World Health Organization in 2019 [1]. In fact, 55% of lung cancer deaths in women and over 70% of lung cancer deaths in men are due to smoking [2]. Cigarette smoking does increase reactive oxygen species and thin which occurrence of oxidative stress playing a critical role in the initiation, promotion, and invasiveness of lung cancer.

Carotenoids are pigments synthesized mostly by plants and they exert important biological functions including scavenging reactive oxygen species [3,4]. Base excision repair is responsible for repairing most of endogenous DNA damage including oxidations and single-strand breaks [5]. DNA glycosylases including 8-oxoguanine glycosylase (OGG1) and Ndi-like DNA glycosylases are a family of enzymes involved in the recognition of BER and excision of damaged base.

We hypothesize that carotenoids can mediate chemoprotective effects by suppressing oxidative DNA damage.

Methods
In this study, human alveolar epithelial cells (A549) were seeded in 6-well plates and pre-treated with various doses (1 nM, 10 nM, 100 nM, 1 µM, & 10 µM) of ATRA, β-carotene, and lycopene for 24 hours. The smoking chamber exposed A549 cells to cigarette smoke for 45 minutes.

Results

Lycopene inhibited smoking-induced oxidative stress
OxyBlot analysis compared the levels of protein oxidation between non-smoking (NS) to smoking (S) A549 cells.
- NS cells: No protein carbonization formation
- S cells: significant increase in protein oxidation
- Oxidation w/ lycopene treatment at 1 nM and 10 nM, but not at higher dosages

Lycopene increased base excision repair in smoking cells

- S cells: ↑ OGG1 & NEIL1 protein levels w/ lycopene treatment at 1 nM, but not at other dosages.
- Expression restoration in S cells ≠ NS cells (P < 0.01).

Lycopene increased base excision repair in smoking cells: OGG1 & NEIL-1/2/3

- NS cells: ↑ OGG1 w/ lycopene treatment at 1 nM, 10 nM, 100 nM, and 1 µM.
- S cells: ↑ NEIL1 w/ lycopene treatment at 10 nM & 100 nM; ↑ NEIL2 w/ lycopene treatment at all dosages.

Lycopene increased base excision repair in smoking cells: Connexin-43

- S cells: ↑ Connexin-43 protein levels w/ lycopene treatment at 1 nM, but not at other dosages.
- Expression restoration in S cells ≠ NS cells (P < 0.01).

Results (cont.)

Lycopene uptake increased in smoking cells

- S cells: ↑ mRNA level of sr-b1 ⇒ carotenoid uptake under oxidative stress
- ↓ RARβ protein in Vehicle-S group, compared to Vehicle-NS group (P = 0.06); attenuated w/ lycopene treatment

Lycopene treatment at a lower dosage could inhibit smoking-induced oxidative stress and promote genome stability. As expected: smoking significantly increased oxidative stress, inhibited by lycopene as the anti-oxidative capacity was highest at 100 nM. In cigarette smoking cells, lycopene increased, OGG1 expression at 1 nM, 10 nM, 100 nM, & 1 µM, but not at 10 µM. Lycopene also increased NEIL1, NEIL2 & NEIL3 protein levels at 10 nM and 100 nM, suggesting that lycopene exerted an anti-oxidant effect at lower doses. In addition, lycopene treatment restored connexin-43 protein expression at 1 nM. Intriguingly, we found at lower concentrations, lycopene treatment in S cells promoted OGG1 expression to an even higher extent compared with NS cells, indicating that lycopene initiated DNA repair more efficiently under oxidative stress. Of note, ATRA and BC did not show anti-oxidant efficacy in our study.

References