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LUNG DISEASE

Antioxidant protection against cigarette smoke

Chronic obstructive pulmonary disease (COPD), which is predominantly induced by smoking, is a leading cause of death in many countries. However, current treatments are primarily symptomatic. Now, reporting in *PNAS*, Sussan *et al.* have shown that pharmacological activation of a transcription factor that controls multiple antioxidative genes confers protection to mice during chronic exposure to cigarette smoke (CS), suggesting an approach to treat patients with COPD.

Nuclear erythroid 2 p45 related factor 2 (NRF2), a redox-sensitive transcription factor, mediates an adaptive response to oxidative stress by upregulating genes coding for more than 100 antioxidative and cytoprotective enzymes. Two lines of evidence have recently highlighted the importance of NRF2 in COPD, in which oxidative stress induced by CS plays a key part. First, lung tissue and alveolar macrophages from patients with advanced COPD exhibit decreased NRF2 activity, suggesting that loss of NRF2-mediated protection could be important in the irreversible destruction of the alveoli (emphysema) in such patients. Second, transgenic mice lacking this transcription factor have more severe emphysema and inflammation following chronic CS exposure than do wild-type mice.

To investigate the therapeutic potential of targeting NRF2 in COPD, the authors used a synthetic triterpenoid known as CDDO-Im, which is a potent small molecule activator of NRF2 signalling. When administered via the diet to mice during 6 months of exposure to CS, CDDO-Im provided significant protection against the alveolar destruction that was observed in mice not receiving the drug. Furthermore, it reduced pulmonary hypertension and prevented decline in right ventricular function, which are common complications linked with emphysema in COPD and contribute significantly to COPD-related mortality.

CDDO-Im has been shown to affect other signalling pathways in addition to NRF2. However, the benefit conferred by CDDO-Im in the study by Sussan *et al.* was shown to be mediated specifically by the NRF2 pathway, as $Nrf2^{-/-}$ mice were not protected by the drug from the effects of CS exposure. In addition, gene expression profiling revealed that the upregulation of several antioxidative NRF2 target genes induced by CS was further enhanced by CDDO-Im in $Nrf2^{+/+}$ mice, but not in their null-gene counterparts. Finally, it was found that CS-induced levels of alveolar apoptosis and oxidative stress were attenuated by CDDO-Im in an NRF2-dependent manner.

These experiments highlight the potential utility of activating existing protective mechanisms orchestrated by NRF2 for the treatment of COPD. Importantly, a drug that is chemically closely related to CDDO-Im is currently in clinical trials for cancer, supporting the viability of evaluating CDDO-Im in COPD patients.

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ORIGINAL RESEARCH PAPER Sussan, T. E. *et al.* Targeting Nrf2 with the triterpenoid CDDO-imidazolide attenuates cigarette smoke-induced emphysema and cardiac dysfunction in mice. *Proc. Natl Acad. Sci. USA* **106**, 250–255 (2009)