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THYROID FUNCTION

Thyroid hormone therapy resolves pulmonary fibrosis in mice

Idiopathic pulmonary fibrosis (IPF) is the scarring and destruction of the lung caused by the accumulation of excessive amounts of extracellular matrix, which is secreted by abnormally activated alveolar epithelial cells. Following up on their observation that the expression of *DIO2* — which encodes the enzyme that converts T_4 into T_3 — is markedly increased in the lungs of patients with IPF, Guoying Yu, Argyris Tzouvelekis, Naftali Kaminski and colleagues have used thyroid hormone therapy to resolve established fibrosis in two mouse models of lung fibrosis.

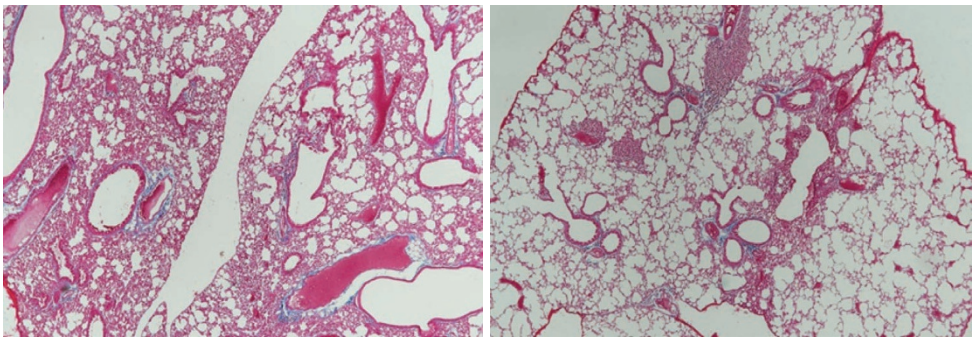
"Following the discovery that mitochondria were abnormal in the lungs of patients with IPF, we were inspired to look for other metabolic genes that are altered in IPF and discovered that the expression of *DIO2*, which encodes type II iodothyronine deiodinase (DIO2), was increased," explains Kaminski. "To better understand the role of *DIO2* in IPF, we formed a collaboration with Antonio Bianco and discovered that *Dio2* knock-out mice were prone to pulmonary fibrosis, which led to the idea that thyroid hormone might be protective in IPF."

> Naftali Kaminski and colleagues have used thyroid hormone therapy to resolve established fibrosis in two mouse models of lung fibrosis

In their study, the authors used two mouse models of pulmonary fibrosis, the bleomycin model and a genetically inducible model. To assess the effect of thyroid hormone on lung fibrosis, Kaminski and colleagues treated mice that had a large amount of fibrotic tissue in their lungs. To avoid the risk of off-target effects of thyroid hormone on the heart and muscle tissue, thyroid hormone was delivered to the lungs in an aerosolized form. Importantly, the authors did not observe an increase in the levels of thyroid hormone in the blood of treated mice when using this delivery method.

"We found that thyroid hormone therapy, as well as treatment with sobetirome (a well-characterized thyroid receptor agonist) resolved established fibrosis in both mouse models of lung fibrosis," concludes Kaminski. "We are now aiming to better understand the cellular mechanisms of the positive effect of thyroid hormone on pulmonary fibrosis, and are working on developing biomarkers that will help us to identify patients who will benefit from thyroid hormone therapy."

Alan Morris



Aerosolized T_3 therapy (right-hand panel) resulted in significantly lower pulmonary fibrosis, as demonstrated by weaker Masson's trichrome staining in comparison with mice treated with doxycycline and vehicle (left-hand panel). Reprinted with permission from Yu, G. *et al. Nat. Med.* http://dx.doi.org/10.1038/nm.4447, Macmillan Publishers Limited.

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