

Mevalonate signaling, COPD and cancer: the statins and beyond

Raewyn J Hopkins, Robert P Young

Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand

Correspondence to

Robert P Young, Faculty of Medical and Health Sciences University of Auckland Auckland New Zealand ; roberty@adhb.govt.nz

Accepted 12 January 2019
Published Online First
20 February 2019

ABSTRACT

Evidence suggests that smoking confers a persistent and/or exaggerated inflammatory response in the lungs that, with underlying genetic susceptibility, may result in lung remodeling and impaired repair. The innate immune response to smoking described above, which is modified by the mevalonate pathway, provides a plausible pathogenic link between the development of chronic obstructive pulmonary disease and lung cancer. The mevalonate pathway modifies innate responsiveness through important intracellular signaling molecules called guanine phosphate transferases (GTPases) such as Rho-A. Smoke exposure activates cell surface proteins which, through the mediating influence of GTPases, then modifies the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) its downstream effects on genes underlying innate immunity, neutrophilic inflammation and carcinogenesis. The mevalonate pathway is modifiable through the enzyme 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMGCo-A) reductase. This enzyme controls the rate limiting step of the mevalonate pathway and is subject to inhibition by statin drugs (HMGCo-A reductase inhibitors) and small chain fatty acids derived from high dietary fiber intake. This inhibitory effect dampens the innate immune response to smoking and may modify pulmonary inflammation and lung remodeling. This article is a symposia summary outlining the preclinical and clinical data suggesting that statins and a high-fiber diet may have a chemopreventive effect on lung cancer.

INTRODUCTION

There is growing evidence that persisting and/or exaggerated inflammation in the lungs, initiated by smoking and upregulated through genetic susceptibility, may underlie lung remodeling and impaired repair that characterizes smoking-related lung disease.¹⁻³ This presentation summary proposes that through well-recognized modifying effects from the mevalonate pathway, the innate immune response to chronic smoking contributes significantly to the development of chronic obstructive pulmonary disease (COPD) and lung cancer (figure 1).²⁻⁶ The mevalonate pathway produces important intracellular signaling molecules called guanine phosphate transferases (GTPases) such as Rho-A.^{2,4-6} It is generally accepted that chronic

smoke exposure activates cell surface proteins on both epithelium and immune cells, which then modify the activation of NFκB and its downstream effects on the expression of genes of the innate immune system.^{2,4} The expression of these genes, encoding cytokines of the innate immune system, is modified by the action of the GTPases derived by the mevalonate pathway.² This observation has relevance to COPD and lung cancer because the mevalonate pathway is readily modified through inhibition of the enzyme 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMGCo-A) reductase.⁷⁻²² This enzyme controls the rate limiting step of the mevalonate pathway and is subject to inhibition by statin drugs and small chain fatty acids derived from high dietary fiber intake (figure 1 and figure 1 of ref 22).^{2,7-22} Other modifiers of the inflammatory cytokines underlying the innate immune response may also play a role.²³⁻²⁵ The overriding impression is that by dampening the innate immune response to smoking, and inhibiting the pulmonary inflammatory response that follows, lung damage can be attenuated.^{2,8,26,27} Such an action might slow the progression of COPD and reduce the tendency to the development of lung cancer.¹⁰

Dampening the innate immune response

One possible mechanism whereby smoking affects the lungs is through the activation of cell surface receptors and the phosphoinositide 3-kinase (PI3K) or related immune pathways.^{2,23-25} Although several receptors are implicated (eg, epidermal growth factor receptor (EGFR) and other growth factor receptors), the cholinergic acetylcholine receptor that binds nicotine in the bronchial epithelium has been implicated by in vitro and genetic epidemiologic studies.^{28,29} Activation of these pathways, which underlie the innate immune system, result in an increased expression of inflammatory cytokines including interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor-α (TNFα). These cytokines play an important role in the inflammatory response, tissue repair and cell death. Collectively clinical, preclinical and epidemiologic studies implicate these inflammatory cytokines in the development of COPD and lung cancer, in particular IL-1 and IL-6.^{2,7,8,23,24,30,31} Similarly, there is growing evidence that the reported 2-4 fold higher risk of lung cancer in current or former



© American Federation for Medical Research 2019. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Hopkins RJ, Young RP. *J Investig Med* 2019;**67**:711-714.

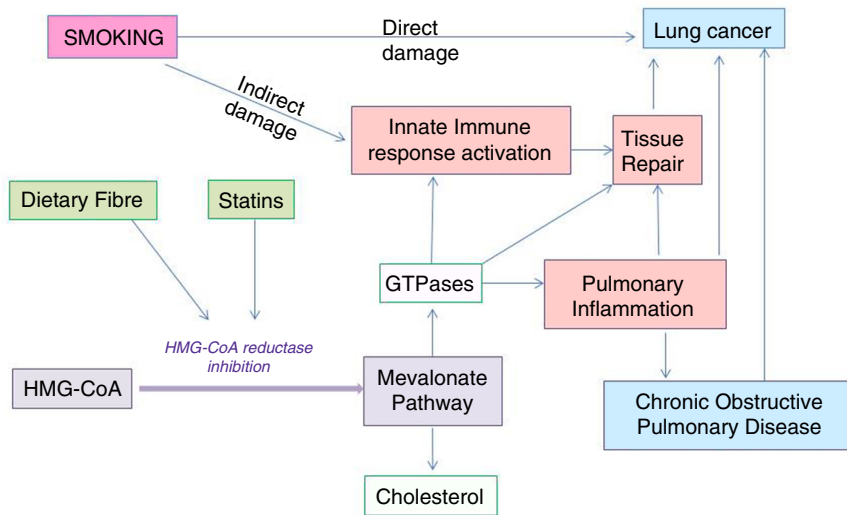


Figure 1 Proposed relationship between the mevalonate pathway, smoking, chronic obstructive pulmonary disease and lung cancer.

smokers with COPD is secondary to the effects of smoking on these overlapping immune pathways.³ This raises the interesting hypothesis that some inhibition of the innate immune system might delay or prevent the development of COPD or lung cancer.¹⁴

Statins and cancer

Evidence suggesting that inhibition of the innate immune system might attenuate the development of lung cancer comes from many scientific studies, in particular two seminal studies.^{7,32} The first study showed that people taking statins have a 20%–30% reduction in smoking-related cancers.^{14,32} Statins are drugs that inhibit the enzyme 3-hydroxy-3-methyl-glutaryl-Coenzyme (HMGCo-A) reductase. This enzyme controls the rate limiting step of the mevalonate pathway through inhibition of the synthesis of molecular signaling molecules called GTPases. Inhibition of GTPases by statins reduces the expression on IL-6 by 30%–50% and may confer an antiproliferative effect. This statin effect is thought to be mediated through an IL-6 trans-signaling pathway and not through direct antagonism of the IL-6 receptor.²⁰ This is important because in vitro studies have shown that upregulation of Rho-A (GTPase) has been linked to both COPD and lung cancer. The second study was a large randomized control trial of dual IL-6 and IL-1 inhibition in high-risk cardiovascular patients.⁷ Those on the IL-1 inhibitor had a 40%–50% reduction in lung cancer incidence compared with the placebo group over the 4 years of follow-up (figure 2). This study suggests that when combining IL-6 and IL-1 inhibition,⁷ the progression to lung cancer in smokers was delayed or prevented and that dampening the innate immune system conferred some beneficial effects on lung carcinogenesis. However, this benefit was off-set by an increase in sepsis related deaths (table 1). In addition, large observational studies have suggested that reduction in lung cancer in those taking statin therapy may be in the order of 30%–50%.¹⁰ Collectively these studies support the hypothesis that dampening of the innate immune response to smoking-related inflammation may reduce the development of lung cancer.

Statins in COPD

Recently, two small randomized studies in patients with COPD have shown biopsy evidence that after statin therapy, there was a reduction in epithelial inflammation of the lung compared with baseline (pretreatment) and not seen in those on placebo.^{30,31} This provides direct evidence of a pulmonary benefit directly conferred by statins and might explain the numerous studies suggesting a reduction in exacerbations of COPD and mortality in patients with COPD taking statins compared with those not.^{14,33–35} We have suggested that the relatively poorer outcomes from those with COPD not on statins is due to unrecognized cardiorespiratory disease (the ‘unhealthy non-user effect’).³⁵ Indeed, it has been known for decades that current or former smokers with impaired lung function (characteristic of COPD) have premature death from cardiovascular, respiratory and cancer causes.³ We and others have shown that as lung function declines, (higher GOLD grade), there is a comparable increased risk of lung cancer incidence, lung cancer deaths and cardiovascular deaths.^{3,36} This observation leads us to suggest that the innate immune response characterized by an increase in systemic inflammatory markers such as IL-6 and CRP, are associated with an increased risk of COPD, coronary heart disease and lung cancer. It is on this basis that statin-based modification of the mevalonate pathways may reduce the incidence of these complications from smoking. Other benefits attributed to statin therapy includes an antioxidant and antiproliferative effect.^{8,10}

Fiber, the gut microbiome, COPD and lung cancer

We and others have proposed that the gut microbiome is also able to moderate the innate immune system and, through this mechanism, moderate the effect of smoking on the lung.^{8,37,38} Numerous studies have shown that diets high in fiber reduces the risk of COPD and death from respiratory disease or smoking-related cancers.^{8,37,38} High-fiber diets promote the growth of gut bacteria known to secrete anti-inflammatory molecules (small chain fatty acids) which

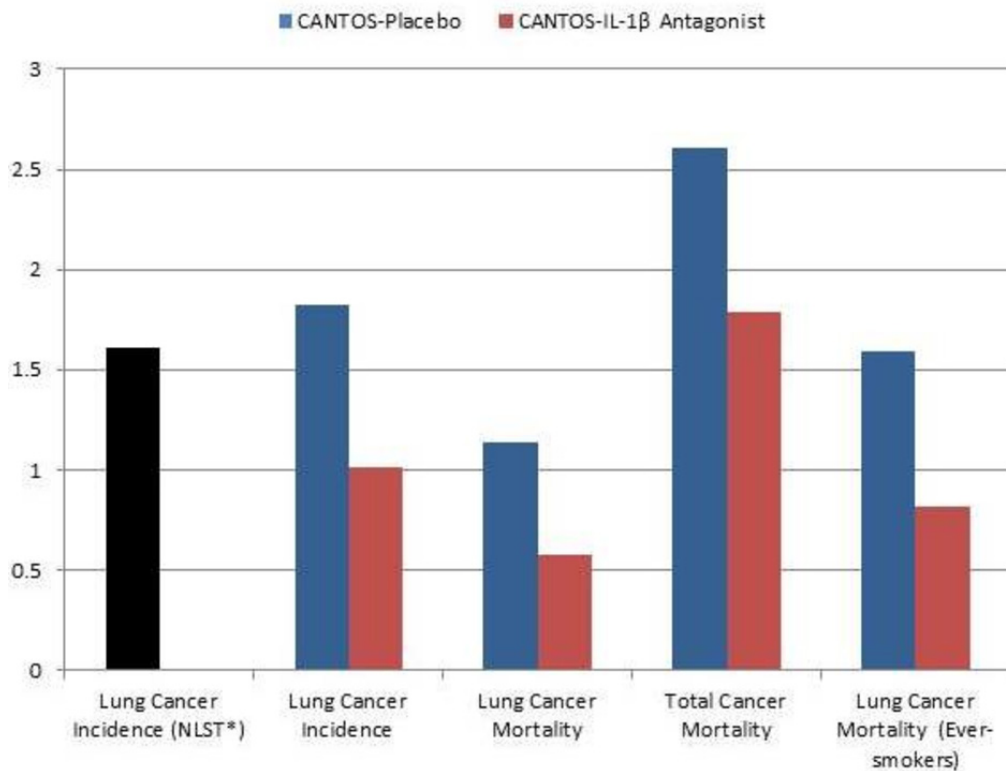


Figure 2 Absolute rates of lung cancer incidence and mortality in the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)⁷ relative to lung cancer incidence during the follow-up interval 3–4 years of the NLST* CXR arm. CXR, chest X-ray; NLST*, National Lung Screening Trial is the largest lung cancer screening trial to date and reported a 20% reduction in lung cancer mortality through the identification and surgical treatment of early stage non-small cell cancer. Over the same duration of follow-up in the CXR arm of the NLST, we found a comparable incidence of lung cancer to that in the placebo arm of CANTOS (1.61% and 1.82% respectively).³⁴

are absorbed into the portal circulation and then the system circulation.⁸ One of these small chain fatty acids (butyrate) inhibits the mevalonate pathway in the liver.¹⁵ Limited evidence suggests that the liver plays a modifying role in lung infection through dampening of the innate immune response to infection.²¹ This is notable because high-fiber diets are associated most dramatically with a reduction in deaths from infection where pneumonia and multiorgan dysfunction syndrome are prevalent. These diseases are characterized by an excessive innate immune response where elevations of the inflammatory cytokines correlate

with mortality. Smaller reduction in respiratory deaths and cardiovascular deaths are reported, along with smoking-related cancers.⁵ We conclude that a high-fiber diet is associated with significant reductions in COPD-related symptoms, COPD and respiratory deaths. Further animal studies are needed to identify the mechanism underlying this fiber–gut–smoking interaction where the mevalonate pathway and innate immune responsiveness may well play important parts.

Summary

In summary, we suggest there exists growing and consistent evidence that dampening of the innate immune response can improve outcomes in those with COPD. This might be achieved through diet or drugs modifying the mevalonate pathway and opens up a plethora of possible preventive approaches to smoking-related lung disease to augment existing smoking cessation interventions.

Contributors RJH and RPY contributed equally to the preparation of this report.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Disclaimer RJH will receive a travel scholarship to attend the Experimental Biology Conference.

Competing interests None declared.

Table 1 A comparison of observed minus expected outcomes in relation to cause-specific mortality (data sourced from Ridker *et al*)⁷

Cause of death	Deaths in placebo* (n=3344 total)	Death in treated (n=6717 total)	Expected deathst	Observed-expected (difference [%])
Lung cancer	38	39	77	-38 (-49)
Other cancers	43	76	86	-10 (-12)
Sepsis	23	78	46	+32 (+70)
Cardiovascular	182	319	366	-47 (-13)
Other/unknown	89	193	178	+15 (+8)
Total	375	705	753	-48

The absolute number of expected deaths in the treated arm were calculated according to deaths in the placebo arm. These were estimated to be approximately twofold that in the placebo arm.⁷

Patient consent for publication Not required.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES

- 1 Baines KJ, Simpson JL, Gibson PG. Innate immune responses are increased in chronic obstructive pulmonary disease. *PLoS One* 2011;6:1–8.
- 2 Young RP, Hopkins RJ. The mevalonate pathway and innate immune hyper-responsiveness in the pathogenesis of COPD and Lung cancer: potential for chemoprevention. *Curr Mol Pharmacol* 2017;10:46–59.
- 3 Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. *Eur Respir J* 2007;30:616–22.
- 4 Touge H, Chikumi H, Igishi T, et al. Diverse activation states of RhoA in human lung cancer cells: contribution of G protein coupled receptors. *Int J Oncol* 2007;30:709–15.
- 5 Walker K, Olson MF. Targeting Ras and Rho GTPases as opportunities for cancer therapeutics. *Curr Opin Genet Dev* 2005;15:62–8.
- 6 Swanson KM, Hohl RJ. Anti-cancer therapy: targeting the mevalonate pathway. *Curr Cancer Drug Targets* 2006;6:15–37.
- 7 Ridker PM, MacFadyen JG, Thuren T, et al. Effect of interleukin-1 β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;390:1833–42.
- 8 Young RP, Hopkins RJ, Marsland B. The Gut-Liver-Lung Axis. Modulation of the Innate Immune Response and its possible Role in Chronic Obstructive Pulmonary Disease. *Am J Respir Cell Mol Biol* 2016;54:161–9.
- 9 Young RP, Hopkins R, Eaton TE. Potential benefits of statins on morbidity and mortality in chronic obstructive pulmonary disease: a review of the evidence. *Postgrad Med J* 2009;85:414–21.
- 10 Young RP, Hopkins R, Eaton TE. Pharmacological actions of statins: potential utility in COPD. *Eur Respir Rev* 2009;18:222–32.
- 11 Janda S, Park K, FitzGerald JM, et al. Statins in COPD. *Chest* 2009;136:734–43.
- 12 Dobler CC, Wong KW, Marks GB, et al. and COPD: a systematic review. *BMC Pulm Med* 2009;9:1–12.
- 13 Marin L, Colombo P, Bebawy M, et al. Chronic obstructive pulmonary disease: patho-physiology, current methods of treatment and the potential for simvastatin in disease management. *Expert Opin Drug Deliv* 2011;8:1205–20.
- 14 Young RP, Hopkins RJ. Update on the potential role of statins in chronic obstructive pulmonary disease and its co-morbidities. *Expert Rev Respir Med* 2013;7:533–44.
- 15 Marciel V, Delvin E, Garofalo C, et al. Butyrate impairs lipid transport by inhibiting microsomal triglyceride transfer protein in Caco-2 cells. *J Nutr* 2003;133:2180–3.
- 16 Zeki AA, Franzi L, Last J, et al. Simvastatin inhibits airway hyperreactivity: implications for the mevalonate pathway and beyond. *Am J Respir Crit Care Med* 2009;180:731–40.
- 17 Ma Y, Hébert JR, Li W, et al. Association between dietary fiber and markers of systemic inflammation in the Women’s Health Initiative Observational Study. *Nutrition* 2008;24:941–9.
- 18 Hodge DR, Hurt EM, Farrar WL. The role of IL-6 and STAT3 in inflammation and cancer. *Eur J Cancer* 2005;41:2502–12.
- 19 Schafer ZT, Brugge JS. IL-6 involvement in epithelial cancers. *J Clin Invest* 2007;117:3660–3.
- 20 Arnaud C, Burger F, Steffens S, et al. Statins reduce interleukin-6-induced C-reactive protein in human hepatocytes: new evidence for direct antiinflammatory effects of statins. *Arterioscler Thromb Vasc Biol* 2005;25:1231–6.
- 21 Hilliard KL, Allen E, Traber KE, et al. The Lung-Liver Axis: a requirement for maximal innate immunity and hepatoprotection during pneumonia. *Am J Respir Cell Mol Biol* 2015;53:378–90.
- 22 Shaykhi R, Crystal RG. Innate immunity and chronic obstructive pulmonary disease: a mini-review. *Gerontology* 2013;59:481–9.
- 23 Barnes PJ. Chronic obstructive pulmonary disease: effects beyond the lungs. *PLoS Med* 2010;7:e1000220.
- 24 Agustí A, Edwards LD, Rennard SI, et al. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012;7:1–10.
- 25 Young RP, Hopkins RJ. Interleukin-6 and statin therapy: potential role in the management of COPD. *Respir Res* 2013;14:74–5.
- 26 Criner GJ, Connert JE, Aaron SD, et al. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med* 2014;370:2201–10.
- 27 Ingebrigtsen TS, Marott JL, Nordestgaard BG, et al. Statin use and exacerbations in individuals with chronic obstructive pulmonary disease. *Thorax* 2015;70:33–40.
- 28 Niu XM, Lu S. Acetylcholine receptor pathway in lung cancer: new twists to an old story. *World J Clin Oncol* 2014;5:667–76.
- 29 Lam DC, Luo SY, Fu KH, et al. Nicotinic acetylcholine receptor expression in human airway correlates with lung function. *Am J Physiol Lung Cell Mol Physiol* 2016;310:L232–L239.
- 30 Mroz RM, Lisowski P, Tycinska A, et al. Anti-inflammatory effects of atorvastatin treatment in chronic obstructive pulmonary disease. A controlled pilot study. *J Physiol Pharmacol* 2015;66:111–28.
- 31 Manechotesuwan K, Kasetsinsombat K, Wongkajornsilp A, et al. Simvastatin up-regulates adenosine deaminase and suppresses osteopontin expression in COPD patients through an IL-13-dependent mechanism. *Respir Res* 2016;17:104.
- 32 Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. *N Engl J Med* 2012;367:1792–802.
- 33 Zhang W, Zhang Y, Li CW, et al. Effect of statins on COPD: a meta-analysis of randomized controlled trials. *Chest* 2017;152:1159–68.
- 34 Li WF, Huang YQ, Huang C, et al. Statins reduce all-cause mortality in chronic obstructive pulmonary disease: an updated systematic review and meta-analysis of observational studies. *Oncotarget* 2017;8:73000–8.
- 35 Young RP, Hopkins RJ, Agustí A. Statins as adjunct therapy in COPD: how do we cope after STATCOPE? *Thorax* 2014;69:891–4.
- 36 Hopkins RJ, Duan F, Chiles C, et al. Airflow limitation confers the same risk of cardiovascular death as diabetes in high risk smokers in the NLST-ACRIN study of the NLST. (N=10,054). *Am J Respir Crit Care Med* 2018;197:A3543.
- 37 Gnagnarella P, Maisonneuve P, Bellomi M, et al. Nutrient intake and nutrient patterns and risk of lung cancer among heavy smokers: results from the COSMOS screening study with annual low-dose CT. *Eur J Epidemiol* 2013;28:503–11.
- 38 Gonzalez CA, Riboli E. Diet and cancer prevention: Contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Eur J Cancer* 2010;46:2555–62.

J Investig Med: first published as 10.1136/jim-2018-000829 on 20 February 2019. Downloaded from file:/ on December 3, 2023 by guest. Protected by copyright.