## Air Pollution–Lung Cancer Link Identified

For more than two decades, scientists have known air pollution is linked to lung cancer in never smokers (LCINS), but not how this happens. The gap between correlation and causation may be narrowing, though, based on findings from researchers at the Francis Crick Institute in London, UK, presented during the ESMO 2022 Congress in Paris, France, September 9–13.

Cancer's classical origin model—carcinogen exposure leads to DNA mutagenesis, with driver events such as KRAS G12C then jump-starting tumor formation—"doesn't quite fit" LCINS, observed lead investigator Charles Swanton, PhD. "This disease has no clear environmental carcinogen–induced DNA mutation signature. So, how do you square the circle here?"

Swanton and colleagues decided to see if an alternative, largely neglected origin model, first proposed by the late Isaac Berenblum in 1947, might come into play. "The idea is that there's a two-step process involved," he explained. "You need an initiator and a promoter, together, to drive clonal outgrowth and tumorigenesis; either alone is insufficient." The team's hypothesis: With LCINS, the initiator could be preexisting somatic mutations in normal tissue, and air pollution could likely be a promoter culprit.

The researchers focused on *EGFR*-mutant non–small cell lung cancer (NSCLC), which commonly occurs in never smokers, and PM2.5—fine, inhalable particulate matter 2.5 micrometers or smaller in size. Across different countries, they documented a strong linear relationship between PM2.5 exposure and cancer incidence. In mice induced with *EGFR* mutations and then regularly exposed to PM2.5, "we saw the same dose-dependent increase in the number of lung tumors," Swanton said, "providing us with proof of causation."

Diving into possible mechanisms, the team probed transcriptional responses in mouse lung epithelial cells after PM2.5 exposure. They observed a transition to more of an alveolar type 2 (AT2) state—AT2 cells are thought to be a progenitor of *EGFR*-mutant NSCLC—as well as increased macrophage recruitment. Monitoring lung epithelial cell growth in an organoid system, "we saw that neither pollution nor *EGFR* mutations were enough to augment their progenitor function; both were required," Swanton said.

Next, collaborating with a group at the University of British Columbia in Vancouver, Canada, the researchers compared their mouse lung data to that of healthy never smokers whose bronchial epithelial cells were analyzed after breathing PM2.5, at levels equivalent to those in major polluted cities, for 2 hours. In both species, the inflammatory cytokine IL1β was upregulated in response to PM2.5.

"This rang bells," Swanton said: IL1β induces a primed AT2 state, and in the CANTOS trial, which evaluated the IL1β inhibitor canakinumab (Ilaris; Novartis) for atherosclerosis, one unexpected side discovery was "a dramatic reduction in lung cancer incidence in a dose-dependent manner" (Cell Stem Cell 2020;27:366–82; Lancet 2017;390:1833–42).

"We think PM2.5 may drive the release of IL1β from macrophages and epithelial cells," Swanton said. Blocking IL1β in mice with *EGFR*-mutant NSCLC "completely abrogated tumor growth," he added, "so this is clearly a smoking gun" when it comes to LCINS.

Notably, too, when the team examined lung samples from 78 healthy never smokers, they found that 15% had *EGFR* mutations (exons 18–21), and 53% had *KRAS* mutations. "These are due to aging and still rare overall—we estimate they're present in roughly 1 in 600,000 cells in the lungs of a 50-year-old," Swanton said. "That said, IL1β released by air pollution may act on these nascent mutations in the wrong cell at the wrong time."

To discussant Suzette Delaloge, MD, of Institut Gustave Roussy in Villejuif, France, "this is a meaningful step forward from epidemiological data, with elegant experiments now demonstrating PM2.5's role in lung cancer." How ubiquitous this mechanism may be and how much PM2.5 exposure is needed and for how long are among the key questions to address, she added.

Whether canakinumab "should be rapidly repositioned" is also worth considering, Delaloge noted, given that "we've learned IL1β is an important, targetable effector. This would help move us toward cancer interception—early detection combined with biomarker-driven prevention therapies—to eradicate cancers before their clinical phase." *–Alissa Poh* ■

**doi:** 10.1158/2159-8290.CD-NB2022-0056

## A Wow for Neoadjuvant ICI in dMMR Colon Cancer

For patients with operable mismatch repair–deficient (dMMR) colon cancer, neoadjuvant immune checkpoint inhibition (ICI) offers significant benefit, according to researchers at the Netherlands Cancer Institute in Amsterdam. Data from their exploratory phase II trial indicate that this approach induces high pathologic response rates, doesn't delay surgery, and keeps recurrence at bay.

Roughly 10% to 15% of colon cancers feature MMR deficiency, said lead investigator Myriam Chalabi, MD, and this subtype is markedly resistant to neoadjuvant chemotherapy, with pathologic response rates of only 5% to 7%. Because advanced dMMR colon cancer is typically responsive to