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* ■

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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

ICI, she and her colleagues decided to evaluate its neoadjuvant potential in patients with early-stage disease.

NICHE-2 enrolled 112 patients, of whom 63% had "bulky tumors commonly involving the abdominal wall, bladder, and pancreas," Chalabi noted. In such cases, "surgeons prefer some type of downstaging beforehand to increase the likelihood of tumor-free resection margins and to limit the extent of surgery needed to achieve that."

Participants received two Bristol Myers Squibb drugs: two cycles of the PD-1 inhibitor nivolumab (Opdivo) and one of the CTLA4 inhibitor ipilimumab (Yervoy). In all, 98% had surgery on schedule—the median time was 5.4 weeks from initial ICI treatment—"which met our primary endpoint of safety and feasibility," she reported during the ESMO 2022 Congress held in Paris, France, September 9–13.

Among 107 patients evaluable for efficacy, 95% achieved a major pathologic response—10% or fewer viable tumor cells in resected tissue—including a pathologic complete response rate of 67%. At a median follow-up of 13.1 months, no disease recurrence was observed. The nivolumab–ipilimumab regimen was well tolerated, with the main side effects being low-grade fatigue, flu-like symptoms, and dry mouth, Chalabi reported.

These findings were met with resounding applause. "You don't see many waterfall plots like this one," remarked discussant James Larkin, PhD, of The Royal Marsden in London, UK. "It's striking data. With very brief treatment, you get a major effect."

A second discussant, Sherene Loi, MD, PhD, of Peter MacCallum Cancer Centre in Melbourne, Australia, agreed that "these are outstanding results in a biomarker-selected population." Neoadjuvant ICI "is likely more efficacious than an adjuvant strategy for facilitating antitumor T-cell responses," she said, "and it should be considered for all cancers in the early-stage curative setting."

How long ICI should be given before and, if necessary, after surgery will be critical to address, Loi observed. The duration "has largely been arbitrary," differing from one study to the next, but "with NICHE-2, we've seen that less may be enough in the most responsive tumors." Determining "what's optimal is an important clinical question" with implications for women of reproductive age—for instance, in preclinical models, "just one cycle of ICI reduces ovarian reserves," she said, "which could influence fertility and result in premature menopause" (Nat Cancer 2022;3:1–13).

As well, following neoadjuvant ICI, "might there be a subset of patients who could avoid surgery altogether?" Larkin wondered. This concept, known as organ sparing or preservation, is gaining traction in rectal cancer, he noted, in which surgery's functional and quality-of-life consequences are significant, even lifelong.

"We could assess organ sparing's feasibility in our future studies," Chalabi agreed. Better biomarkers of ICI efficacy are first needed, however—a gap she hopes her team's translational research efforts, using circulating tumor DNA dynamics and novel imaging techniques, can help fill.

Meanwhile, NICHE-2's disease-free survival data at 3 years are expected in 2023, Chalabi said, and "the future has never been brighter" for patients with early-stage dMMR colon cancer. "Neoadjuvant ICI has the potential to become standard care, and I urge pharma to strive for registration as quickly as possible." –*Alissa Poh* ■

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Myriad Cancers Found with One Blood Draw

Multicancer early detection (MCED) by dint of a simple blood assay is still in its infancy and not yet ready for broad deployment. However, data from a prospective study of one such test, Galleri (GRAIL), show glimpses of potential and suggest that MCED may one day fundamentally change cancer screening as we know it.

Through next-generation sequencing and machine learning, Galleri "looks at methylation patterns on cell-free DNA in the blood, then returns a binary result," explained Deborah Schrag, MD, of Memorial Sloan Kettering Cancer Center in New York, NY. "Either no cancer is found, or if there is a signal, the assay goes on to predict the most likely tumor type."

During the ESMO 2022 Congress in Paris, France, September 9–13, Schrag presented final results from the PATHFINDER study, which enrolled 6,621 participants age 50 or older to be tested with Galleri. "Our motivation was to understand the clinical experience of MCED," she said. "What diagnostic evaluations are precipitated by the receipt of a 'signal detected' result? What are [Galleri's] performance characteristics?"

The vast majority of PATHFINDER's participants received negative results, Schrag said. In all, 92 tested positive, "amounting to a signal detection rate of 1.4%." After undergoing CT, MRI, or PET, 57 turned out to be false positives. Of the remaining 35, Galleri definitively predicted the origin of malignancy in 34, with an overall accuracy rate of 97.1%. "This helps guide diagnostic workups," Schrag added. "If the prediction is head and neck, for instance, physicians could start with an oropharyngeal exam and perhaps an ENT referral."

Among these 35 participants, 18 were diagnosed with solid tumors and 17 with blood malignancies. One was found to have both breast and uterine cancers. Roughly 40% had early-stage disease, and nearly 75% of the diagnoses "were cancers such as pancreatic and ovarian for which there is no standard screening," Schrag said.

To discussant Federica Di Nicolantonio, PhD, of the University of Turin in Italy, although the number of false positives with PATHFINDER was not unreasonable, more work is needed to figure out why this happens and to reduce its occurrence. The same is true with false negatives—there were 86 in the study—and she wondered "if it might be due to nonshedding tumors or fast-growing disease that wasn't even present at the time of testing."

"We're still far from perfect in this setting [MCED]," Di Nicolantonio remarked, "but taking a long-term