News & views

Tumour biology

Air pollution's role in the promotion of lung cancer

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Air pollution is associated with the development of lung cancer. Analysis of clinical samples and mouse cancer models suggests that inflammation and a tumour-promotion process induced by polluted air are the major culprits. **See p.159**

The mechanisms underlying how air pollution can contribute to lung cancer have been hard to pinpoint. On page 159, Hill *et al.*[1] report studies of human lung samples and mouse cancer models that shed light on this issue.

Oxygen is essential for many forms of life. Yet despite its importance, humans have contaminated the atmosphere with a wide variety of pollutants. The World Health Organization has concluded that this dangerous trajectory has resulted in an increased risk of lung cancer, with an estimated 250,000 worldwide deaths per year attributable to atmospheric pollution[2]. The best long-term solution is to cease this pollution, but doing so presents major challenges, and it is unlikely that such an approach will bear fruit in the short term.

Studies have therefore been initiated to try to understand how pollution induces lung cancer, and to find ways to prevent exposed individuals from developing the disease. Hill and colleagues present a multidisciplinary analytical and technical tour de force that helps to show how pollution interacts with lung cells to promote the changes that eventually result in malignancy (Fig. 1).

The authors carried out a detailed analysis of the epidemiology of air pollution and its links to lung cancer in several groups of patients in the United Kingdom, South Korea, Taiwan and Canada. The authors also searched for differences between tumours linked to air pollution and those associated with cigarette smoking. This revealed that non-smokers living in highly polluted areas were more likely to develop lung cancers than were non-smokers living in low-pollution areas, although the risk at the individual level is not particularly high, and certainly less than the risk of developing cancer from cigarette smoking.

To determine how air pollution causes cancer, the authors analysed the sequences of tumour DNA samples from non-smokers living in polluted areas, and report that the sequences exhibit few genetic changes called point mutations, which can activate genes known to drive cancer development. The mutations found were those associated with normal processes – essentially resulting from mistakes that occur when DNA is replicated during cell division. By contrast, the DNA of tumours from smokers displays a distinct mutational signature that arises owing to the presence of mutation-inducing components of tobacco smoke.

How does air pollution cause lung cancer in non-smokers if it does not induce the same kinds of mutation that are induced by tobacco smoke, or indeed any notable mutations at all? Two clues from previous work might help to provide an answer.

A 2020 study[3] reported DNA sequencing of mouse tumours induced by exposure to

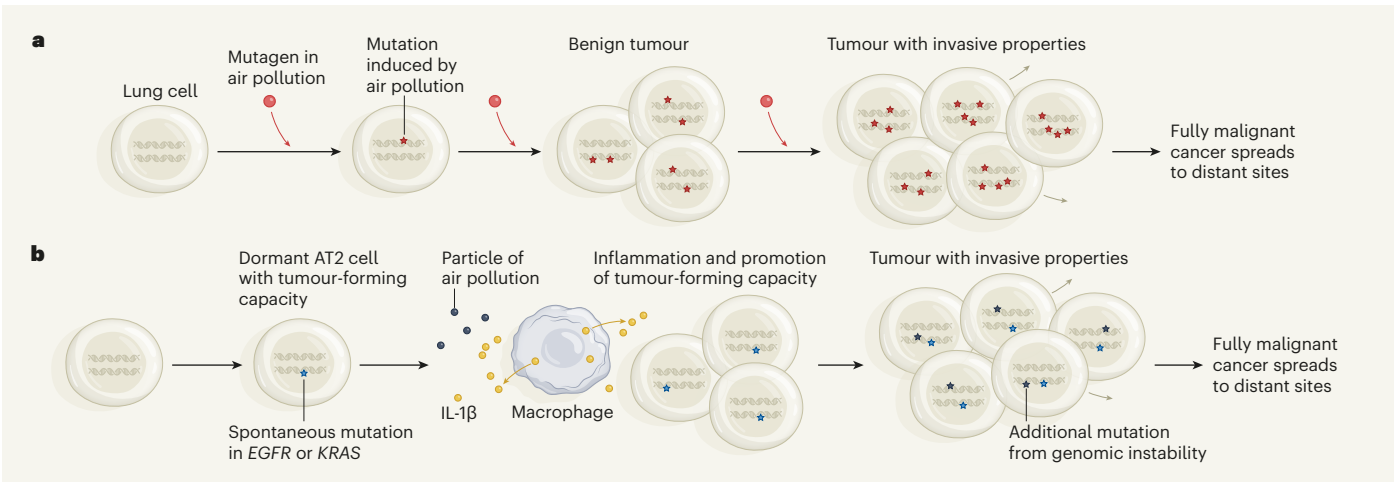

Figure 1 | Alternative models to explain lung cancer development due to air pollution. a, In one model of cancer formation, the mutation-driving mutagen molecules present in polluted air cause the sequential accumulation of mutations in the lungs of exposed individuals. This enables some cells to acquire the necessary number and combination of mutations to progress from a benign tumour through the series of biological steps that lead to full malignancy. **b**, Hill *et al.*[1] present evidence consistent with a model suggesting that particles in air pollution act mainly to promote the proliferation of lung cells that carry pre-existing mutations owing to spontaneous DNA replication errors or chance exposure to a mutagen. These mutations are often in the genes *EGFR* or *KRAS*. The cells in question, such as lung cells called AT2 cells, lie dormant unless activated by factors that stimulate inflammation and cause tissue damage. Pollution can drive the recruitment of immune cells called macrophages into the lungs. Macrophages release the molecule IL-1β and cause inflammation, which promotes cancer formation from dormant cells. Such tumours can acquire more mutations as a result of a rise in proliferation and genomic instability.

20 known or suspected human cancer-causing agents (carcinogens). Those data indicate that only a few of the carcinogens acted as mutagens to increase the number of mutations (the mutation burden) or to induce specific mutational signatures. This suggested that most carcinogens do not have to be strong mutagens to cause cancer. Other work has shown that many mutations, including those linked to the development of cancer, can accumulate in normal human tissue during ageing without causing any obvious cancer-related changes[4]. It seems that highly mutated cells can lie dormant in normal tissue without causing problems until 'awakened' by a process that converts the cells to actively growing early-stage tumours.

Precedent for such a scenario came from studies[5] in the 1940s showing that 'initiated cells' (mutated by mutagens in coal tar, although this was not demonstrated until much later[6,7]) remained dormant in mouse skin for up to one year. However, these cells could be activated to form early-stage tumours by a few weeks of treatment with a 'tumour promoter' – a chemical irritant derived from croton oil. This chemical came to be known as the tumour-promoting agent (TPA), which is an activator of inflammation, proliferation and other hallmarks of cancer[8].

Those previous data raised the possibility that most environmental carcinogens, including those in polluted air, act to promote cells that have pre-existing cancer-initiating (oncogenic) mutations. Indeed, the particulate and chemical constituents of air pollution and tobacco smoke were tested in the 1960s, using the same mouse skin model, and were found to have such promoting activity[9,10]. Cigarette smoke, although clearly a strong mutagen, also induces inflammation and has tumour-promoting activity, possibly explaining why it is such a potent carcinogen. Whether the smoking alternative vaping, also known to induce inflammation, can act in a similar way to air pollution to induce lung cancers remains to be determined[11].

Hill *et al.* used a combination of lung cancer models in mice and human cells grown in 3D cultures (organoids) to test the hypothesis that particulate matter measuring less than 2.5 micrometres, termed $PM_{2.5}$, from air pollution functions in a similar way to TPA, to induce growth of lung cells that carry pre-existing cancer-initiating mutations. Mice with genetically engineered mutations in the gene encoding the epidermal growth factor receptor (EGFR) protein (known to be mutated in some human lung cancers, particularly in non-smokers), or in the *Kras* gene (a commonly mutated gene in lung cancer), developed more-rapidly growing lung tumours after just a few weeks of exposure to $PM_{2.5}$ compared with mice lacking these mutations.

Sequencing of DNA from biopsies of normal lung tissue from individuals, some of whom had been diagnosed with lung or other cancers, detected cells that carried *EGFR* or *KRAS* mutations in 18% and 53%, respectively, of the samples. The most plausible explanation is that humans are susceptible to acquiring mutations spontaneously during the replication of normal lung cells, or through exposure to a mutagen, but that these mutations do not cause immediate disease because a tumour does not start to grow and the tissue structure remains essentially intact. However, for individuals living in areas with air pollution, these cells might breach the barriers that would normally restrain their proliferation, eventually reaching the stage of tumour growth.

These results have major implications for how to think about cancer prevention. A popular model of cancer evolution assumes that tumours arise as a consequence of the inexorable accumulation of mutations, each of which activates a particular stage or signalling pathway that drives cancer progression (Fig. 1a). There is presently nothing that can be done to remove the mutated cells that accumulate in normal tissues, but if there is a promotion stage (Fig. 1b) that influences the rate of cancer development, then inhibition of this stage might be an effective way to prevent cancer.

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Given Hill and colleagues' results showing increased expression of the protein interleukin-1β (IL-1β) during $PM_{2.5}$-induced lung inflammation in mice, and building on a study of human cardiovascular disease showing that an IL-1β-targeting antibody reduces the incidence of lung cancer[12], the authors exposed *Egfr*-mutant mice to $PM_{2.5}$ and to an antibody against IL-1β. This antibody treatment resulted in significant attenuation of lung cancer formation compared with what was observed in mice that didn't receive the antibody. The authors attribute the attenuating effect of antibody treatment to the fact that $PM_{2.5}$ induces sustained inflammation and ensuing recruitment of immune cells called macrophages into the lungs. These macrophages provide signalling molecules, including IL-1β, that can activate some lung stem cells, called AT2 cells, to start growing, particularly if they have *Egfr* mutations.

Prevention of pollution-induced lung cancer by treating millions of exposed individuals worldwide with expensive anti-IL-1β antibodies is not feasible. Nevertheless, the knowledge gained from Hill and colleagues' study might revitalize the search for more-realistic prevention measures, including the possibility of dietary interventions. Some dietary factors reduce the incidence of TPA-promoted skin cancers in mice, in part by inhibiting the expression of IL-1β as well as of other inflammatory mediators[13]. Published work reports hundreds of studies of the prevention of tumour promotion in mouse skin using antioxidant molecules, anti-inflammatory agents or antibodies against various inflammatory mediators.

How can this trove of biological information on tumour promotion best inform human cancer-prevention trials, bearing in mind that past attempts to jump quickly from mouse to human studies without really understanding the mechanisms involved have sometimes led to expensive failures[14]? Benign early-stage growths are not the same as premalignancies that are at high risk of progression, and recognizing and tackling the latter will be crucial for developing effective cancer-prevention measures. Hill and colleagues' results should help to shift the emphasis towards dietary or pharmacological prevention of cancer caused by breathing polluted air, while the public awaits progress in efforts to reduce pollution.

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