

BIOMEDICINE

Do Airborne Particles Induce Heritable Mutations?

Jonathan M. Samet, David M. DeMarini, Heinrich V. Malling

Urban air is contaminated by gaseous and particulate emissions from a variety of sources. Emissions emanate from vehicles, industries, and power stations and also occur naturally. These emissions, as well as their atmospheric transformation products, damage ecological systems and adversely affect public health (1). Airborne particles have been a particular concern because epidemiological findings link current levels of airborne particulate pollutants to a growing list of adverse health effects (1). On page 1008 of this issue, Somers and colleagues (2) extend these observations beyond the effects of particulate matter on somatic cells. They present experimental evidence that airborne particles cause heritable genetic changes in the male mouse germline that can be passed on to the next generation.

By monitoring changes in the size of noncoding tandem-repeat DNA sequences, the authors show that offspring of mice exposed to an industrial location on western Lake Ontario have an increased rate of presumptive mutations and that these genetic changes are paternally derived. Their discovery that the mutation rate could be reduced by ~50% by cleansing the air with a high-efficiency-particulate-air (HEPA) filter suggests that particle-bound mutagens, or the particles themselves, are responsible for the observed, heritable DNA changes. These new findings extend a series of investigations that began with the observation that herring gulls in Hamilton Harbor, Ontario, have a higher rate of minisatellite DNA changes than gulls in rural sites (3). A follow-up experiment with mice showed increased induction of DNA changes in the offspring of mice housed in a polluted location at the harbor compared with control animals housed in an unpolluted location (4).

The new findings imply a remarkable chain of events that begins with ambient particulate pollutants with mutagenic activ-

ity and ends with these compounds (or the particles themselves) causing presumptive, heritable changes (see the figure). Evidence is available for some of the elements in this sequence of events, supporting its plausibility, but gaps in the sequence remain.

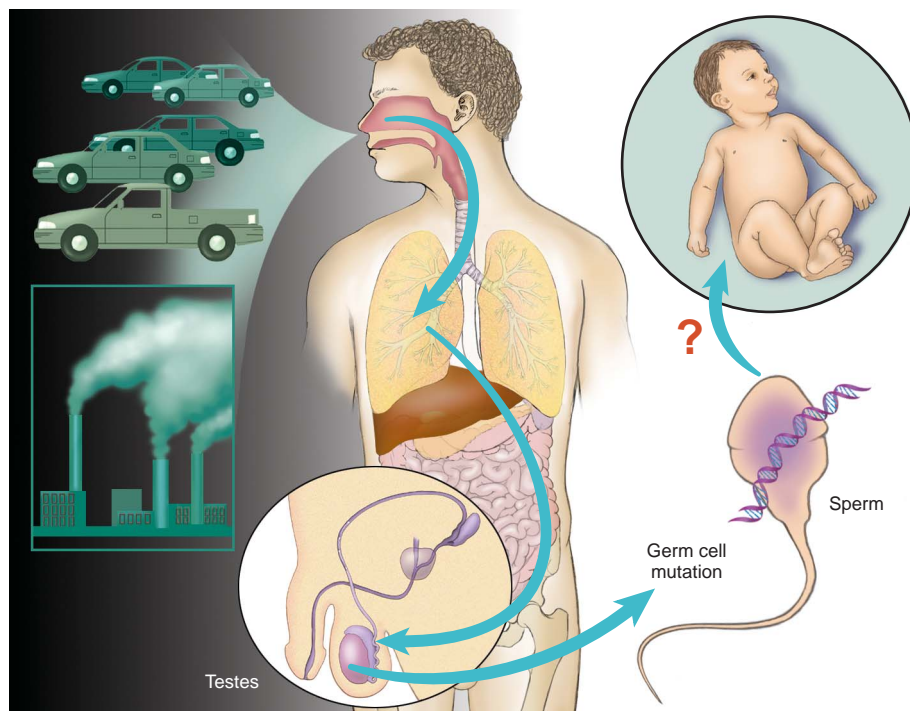
How are somatic cell mutations induced by airborne particles? We know that urban air pollution has mutagenic activity, that this activity is associated with airborne particles, and that air pollution is linked to lung cancer (1). Multiple chemicals, such as polycyclic aromatic hydrocarbons (PAHs), contained within particles or bound to their surfaces are mutagens or carcinogens. Small inhaled particles, which are cleaned from the air by a HEPA filter, penetrate deeply into the lungs, where adsorbed materials enter the blood and become distributed systemically. PAH exposure, whether from tobacco (5) or coal emissions (6), leads to the formation of lung tumors carrying unique sets of muta-

tions. Thus, inhaled combustion emissions and, possibly, polluted urban air generally induce mutations in somatic cells.

How might these inhaled pollutants induce genetic changes in male mouse germ cells? The inhaled toxicants would have to reach the bloodstream, be transported to the liver, possibly be metabolized to DNA-reactive species, be transported to the testis, and finally reach the spermatogonial stem cells. DNA damage could then be processed in the spermatogonial stem cells, resulting in tandem-repeat changes in mature sperm that can be transmitted to the first-generation offspring.

Considering the timing of the exposure and matings described by Somers *et al.* (2), premeiotic germ cells may be the sensitive target for DNA damage by air pollution, as they are for ionizing radiation (7). However, mechanisms for inducing changes in tandem-repeat DNA sequences lie outside the conventional model for the induction of mutations in coding genes and are poorly understood. Changes in these DNA sequences occur at rates much higher than predicted on the basis of mutation rates in coding genes (7).

PAHs bound to particles are a candidate group of chemicals that react with DNA after metabolic activation. PAHs are a compo-



Inhaled air particles and heritable mutations. Airborne particulate pollution is caused primarily by emissions from vehicles, industries, and power stations. Inhalation of airborne particles into the lungs leads to presumptive mutations in mouse male germ cells that can be passed on to the next generation.

J. M. Samet is in the Department of Epidemiology, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD 21205, USA. D. M. DeMarini is at the U.S. Environmental Protection Agency, Research Triangle Park, NC 27711, USA. H. V. Malling is at the National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709, USA. E-mail: jsamet@jhsph.edu

CREDIT: TAINA LITLAK

PERSPECTIVES

ment of emissions from steel mills and vehicle exhaust, primary sources of air pollution in the contaminated Hamilton Harbor location, and they cause germ cell mutations in mammals. PAHs such as benzo(a)pyrene and dimethylbenzanthracene induce dominant lethal mutations in female mice when given by intraperitoneal injection (8), an exposure route of uncertain relevance to inhalation.

New evidence shows that PAHs associated with inhaled particles also may cause changes in humans during development. Pregnant women exposed to elevated levels of particulate matter and carcinogenic PAHs in ambient air have an increased risk of delivering a low-birth weight child compared to women with lower exposures (9). This risk is doubled if the exposure occurs during the first month of pregnancy (10). A link also exists between somatic mutation in newborns and transplacental exposure to common air pollutants, including polycyclic organics (11). Studies in humans indicate that elevated air pollution also may cause DNA damage in male germ cells (12). Evidence on cigarette smoking, another source of exposure to PAHs, suggests the possibility of smoking-associated germ cell mutations (13).

Despite the study's elegant experimental design, the findings by Somers *et al.* (2) should be interpreted with caution. First, their tandem-repeat assay has been validated with only three chemical mutagens, and the transmission of these chemically induced changes to the second-generation offspring has not yet been examined (7). Second, the mutational mechanisms by which these tandem-repeat changes are induced are unclear. The mechanisms operating at some tandem-repeat sequences in mice are fundamentally different from those in humans (7). Nonetheless, the doubling dose for ionizing radiation-induced DNA changes in this assay is similar to that for coding genes in the definitive mouse specific-locus assay for germ cell mutations, despite differences in the absolute mutation frequencies in these two assays.

Although air pollution has dropped substantially in recent decades in the United States and many other developed countries, epidemiological studies continue to show adverse health effects at current levels of particulate matter and ozone (1). Regulations to protect public health have been strengthened because of this and other evidence. The new work now adds another area of potential concern. Confirmation of the Somers *et al.* find-

ings (2) would extend the adverse health effects of air pollution beyond effects on somatic cells in the exposed generation to germ cells—with the attendant implications for health risks to future generations.

References and Notes

1. J. M. Samet, A. J. Cohen, in *Air Pollution and Health*, S. T. Holgate, J. M. Samet, H. S. Koren, R. L. Maynard, Eds. (Academic Press, San Diego, 1999), chap. 36.
2. C. M. Somers, B. E. McCarry, F. Malek, J. S. Quinn, *Science* **304**, 1008 (2004).
3. C. L. Yauk, J. S. Quinn, *Proc. Natl. Acad. Sci. U.S.A.* **93**, 12137 (1996).
4. C. M. Somers *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **99**, 15904 (2002).
5. P. Hainaut, G. P. Pfeifer, *Carcinogenesis* **22**, 367 (2001).
6. D. M. DeMarini *et al.*, *Cancer Res.* **61**, 6679 (2001).
7. C. L. Yauk, *Mutat. Res.* **566**, 169 (2004).
8. J. B. Bishop *et al.*, *Fundam. Appl. Toxicol.* **40**, 191 (1997).
9. F. P. Perera *et al.*, *Environ. Health Perspect.* **111**, 201 (2003).
10. J. Dejmek, I. Solansky, I. Benes, J. Lenicek, R. J. Sram, *Environ. Health Perspect.* **108**, 1159 (2000).
11. F. Perera *et al.*, *Cancer Epidemiol. Biomarkers Prev.* **11**, 1134 (2002).
12. S. G. Selevan *et al.*, *Environ. Health Perspect.* **108**, 887 (2000).
13. D. M. DeMarini, *Mutat. Res.*, in press.
14. We thank R. J. Preston, R. D. Owen, L. D. Claxton, C. L. Yauk, S. D. Perreault, J. B. Bishop, and M. D. Shelby for helpful comments. This article was reviewed at the National Health and Environmental Effects Research Laboratory of the U.S. Environmental Protection Agency and approved for publication.

GEOCHEMISTRY

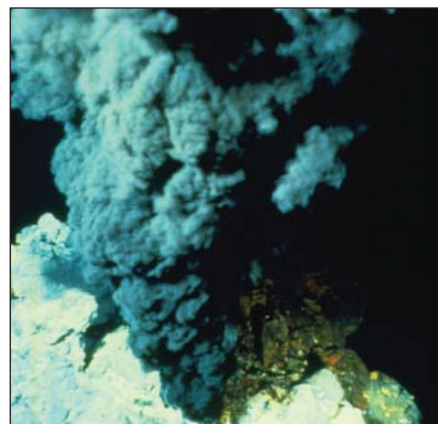
Life's Chemical Kitchen

Barbara Sherwood Lollar

The first photographs from the submersible *Alvin* in 1979 stunned us all. An expedition to the tectonic spreading centers of the East Pacific Rise was staffed by oceanographers and geologists, but few biologists. After all this was an exploration of the deep-sea floor far from the Sun's life-sustaining rays. However, like a scene through Captain Nemo's portals, tube worms, mussels, and clams the size of dinner plates formed part of the macrofauna that testified to a complex biological ecosystem not dependent on photosynthesis (1). What are the recipes for sustaining life in this kind of chemical kitchen? Chemolithotrophic (literally chemical- and rock-consuming) microbes use the reactants provided by cooling basalt flows as substrates to drive a variety of chemical reactions, including methanogenesis, and SO_4^- and S^0 reduction at the high-temperature vents, and oxidation of H_2S , CH_4 , Fe^{2+} , and Mn^{2+} under lower temperature regimes (2). But are there substrates for chemolitho-

trophic microbes away from the hydrothermal vents? On page 1002 in this issue, Foustoukos and Seyfried (3) provide experimental evidence for another possible source of substrates that may serve as key ingredients in the chemolithotrophic deep biosphere.

As the ocean crust cools and ages, seawater and hydrothermal fluids hydrate ultramafic (Mg-, Fe-rich) silicates in the ocean crust to produce serpentinized rocks, Mg- and Fe-hydroxides, and abundant H_2 gas. Production of abiogenic short-chain hydrocarbons such as methane, ethane, and propane by serpentinization has been a subject of debate (4). If H_2 and hydrocarbons from this type of abiogenic water-rock interaction are used as microbial substrates, then chemolithotrophic life may be feasible in parts of the Earth's crust where serpentinized rocks are globally widespread, ranging from the modern seafloor (5) to ancient seafloor deposits in billions-of-years-old Precambrian shield rocks (6). A chemical recipe for life applicable to both the hydrothermal vents and to broader geological environments would have important implications not only for deep-biosphere studies, but also for understanding prebiotic organic synthesis and the emer-



Black smoker vent. View from the deep-submergence vehicle *Alvin* of black "smoke" being emitted by the *Spire* hydrothermal vent on the ocean floor. Known as a "black smoker," the *Spire* pours out a sulfurous mineral-rich fluid from its mound or chimney that is 18 m high. The volcanic fluid bubbles up due to geothermal energy in the Earth's crust, at a temperature of 365°C. Deep-sea vents provide an unusual habitat to some primitive forms of extremophile bacteria and deep-sea crabs that can survive extreme conditions. The *Spire* is located at the Broken Spur Vent Field in the Mid-Atlantic Ridge, 3080 m below sea level.

gence of life in the early Earth (7). In addition, such chemolithotrophic systems may be a terrestrial analog for possible subsurface microbial communities on other planets or moons (8).

The author is in the Stable Isotope Laboratory, Department of Geology, University of Toronto, Toronto, Ontario, Canada M5S 3B1. E-mail: bsllollar@chem.utoronto.ca