Chronic inflammation caused by disease or exposure to dangerous chemicals has long been linked to cancer, but exactly how this process takes place has remained unclear.

Now, a precise mechanism by which chronic inflammation can lead to cancer has been uncovered by researchers at MIT—a development that could lead to improved targets for preventing future tumors.

In a paper published this week in the Proceedings of the National Academy of Sciences, the researchers unveil how one of a battery of chemical warfare agents used by the immune system to fight off infection can itself create DNA mutations that lead to cancer.

As many as one in five cancers are believed to be caused or promoted by inflammation. These include mesothelioma, a type of lung cancer caused by inflammation following chronic exposure to asbestos, and colon cancer in people with a history of inflammatory bowel disease, says Bogdan Fedeles, a research associate in the Department of Biological Engineering at MIT, and the paper’s lead author.

Innate immune response

Inflammation is part of the body’s innate response to invading pathogens or potentially harmful irritants. The immune system attacks the invader with a number of reactive molecules designed to neutralize it, including hydrogen peroxide, nitric oxide and hypochlorous acid.

However, these molecules can also cause collateral damage to healthy tissue around the infection site: “The presence of a foreign pathogen activates the immune response, which tries to fight off the bacteria, but in this process it also damages some of the normal cells,” Fedeles explains.

Researchers have uncovered a way chronic inflammation can lead to cancer. Panel 1 shows a normal DNA base pair of cytosine (C) and guanine (G). In panel 2, inflammation, represented by a red background, damages the base pair. A chlorine atom (Cl) is added to the cytosine, resulting in a cytosine lesion called 5-chlorocytosine. In panel 3, the cytosine lesion is now able to base pair with adenine (A). In panel 4, the adenine directs incorporation of an opposing thymine (T) at the position of the initial (C). Thus, the formation of 5-chlorocytosine in DNA drives the formation of C:G-to-T:A mutations.

Image: Jose-Luis Olivares/MIT

Previous work by Peter Dedon, Steven Tannenbaum, Gerald Wogan, and James Fox—all professors of biological engineering at MIT—had identified the presence of a lesion, or site of damage in the structure of DNA, called 5-chlorocytosine (5ClC) in the inflamed tissues of mice infected with the pathogen Helicobacter hepaticus. This lesion, a damaged form of the normal DNA base cytosine, is caused by the reactive molecule hypochlorous acid—the main ingredient in household bleach—which is generated by the immune system.

The lesion, 5ClC, was present in remarkably high levels within the tissue, says John Essigmann, the William R. (1956) and Betsy P. Leitch Professor in Residence Professor of
Congratulations to Professor **Elizabeth Nolan** who was named the recipient of the 2016 Eli Lilly Award in Biological Chemistry. This Award was presented to Professor Nolan in recognition of her contributions to metal homeostasis and human innate ability.

http://chemistry.mit.edu/nolan-receives-2016-eli-lilly-award-biological-chemistry

Congratulations to Professor **Sangeeta Bhatia** who was named the recipient of the 2015 Heinz Award for Technology, the Economy, and the Employment. Bhatia is recognized for her seminal work in tissue engineering, disease detection, and for her passion in promoting the advancement of women in science, technology, engineering, and mathematics (STEM) fields.


Congratulations to Professor **Edward Boyden** who was honored with the Breakthrough Prize in Life Sciences given for "transformative advances towards understanding living systems and extending human life."


Congratulations to Professor **Jocquin Niles** who was selected as a recipient of a Professor Amar G. Bose Research Grant for the creativity and vision of proposal "Engineering Mutualism: Using malarial organisms for systemically delivering therapeutics."

Congratulations to Professor **Bradley Pentelute** who was selected as the 2015 recipient of the prestigious Novartis Early Career Award in Organic Chemistry. Research in the Pentelute lab entails the use of new chemistry and platforms to solve important problems in chemical biology. We focus on the use of cysteine arylation to generate abiotic macromolecular proteins, the precision delivery of biomolecules into cells, and the development of fast flow platforms to rapidly produce polypeptides.


Congratulations to Professor **Matthew Shoulders** who was named a recipient of the 2015 NIH Director’s New Innovator Award for his project entitled “Continuous Directed Evolution in Biomolecules in Human Cells in Medical Research.”


Congratulations to Professor **Colette Heald** who was awarded the American Geophysical Union (AGU) James B. Macelwane Medal in recognition of “significant contributions to the geophysical sciences by an outstanding young scientist.”


Congratulations to Professor **Jacquin Niles** who was selected as the 2015 recipient of the prestigious Novartis Early Career Award in Organic Chemistry. Research in the Pentelute lab entails the use of new chemistry and platforms to solve important problems in chemical biology. We focus on the use of cysteine arylation to generate abiotic macromolecular proteins, the precision delivery of biomolecules into cells, and the development of fast flow platforms to rapidly produce polypeptides.
Using Microbes to Clean Up Oil Spills
Professor Catherine Drennan and graduate student Michael Funk want energy production and environmental protection to go hand in hand.

Article by Francesca McCaffrey, MIT Energy Initiative

Catherine Drennan, a professor of chemistry and biology, likes to wax poetic about the complex chemistry of microbes. "I think they’re elegant and beautiful," she says. Of course, she also sees their practical applications. "I love the fact that these microbes can be used for bioremediation in hard-to-reach polluted spots," she says. "Normally, cleaning these delicate environments would upset the balance of living organisms there, but microbes offer a natural way to clean things utilizing chemistry."

Drennan and Michael Funk, a graduate student in chemistry, are part of a team testing the nuances of how microbes break down hydrocarbons while metabolizing them for growth and survival. Because hydrocarbons are a natural (and major) molecular component of crude oil, microbes could be aid cleanup efforts following oil spills and other instances of pollution — as long as the microbes’ hydrocarbon metabolism process proceeds smoothly. The first step in that process calls for the microbe to chemically attack the hydrocarbon to generate a more reactive molecule, but some hydrocarbons are challenging to get a handle on.

To learn more about how to circumvent the inert nature of hydrocarbons, Drennan, Funk, and fellow researchers explored the structural basis by which one microbe — the denitrifying bacterium Thauera aromatica — activated and broke down the hydrocarbon toluene.

The details of their findings, which involve the mapping of previously unknown enzymatic structures, were released in a paper this summer in The Journal of Biological Chemistry.

"When you’re thinking about how an organism breaks a carbon source down and then uses that to make energy for itself,” Drennan says, "you think it’s going to take it and pull it apart, but in this case, it makes a bigger molecule first. That’s because the thing that it wants to add into its metabolism and make energy from is so nonreactive that it has to come up with some way to get a handle on it and make it useful.”

Winning combination

The winning combination that enables the breakdown process is the pairing of the enzyme benzylsuccinate synthase (naturally occurring within the microbe) with the substrate molecule fumarate (also present in the microbe) in the presence of toluene. The benzylsuccinate synthase acts as a catalyst, encouraging a reaction between the toluene and the fumarate to generate benzylsuccinate. The conversion of toluene to benzylsuccinate makes it more reactive — as Drennan described above — and the first step in the metabolism process is then possible.

Funk recalls the multi-step process of determining how this enzyme enables the reaction: “A couple of years ago our research revealed the structures of the enzyme benzylsuccinate synthase without anything bound, so that was the first step, to see the overall architecture of the active site. But we still didn’t know how that enzyme would bind to a substrate.”

Funk and Drennan were able to get the substrate fumarate to bind to the enzyme: Fumarate has two carboxyl groups and fits perfectly with the active site. With those two pieces in place, they experimented with different forms of the enzyme until they were able to bind toluene.

Discoveries like this one — which shed light on how hydrocarbons like toluene can be broken down, despite their nonpolar (and therefore usually non-binding) nature — are a critical starting point for more organized efforts in bioremediation (waste management using organisms), Funk says. He is quick to point out, however, that we are still far from any kind of panacea.

"One of the things I didn’t anticipate is how precise the active sites on molecules are,” Funk says. “This enzyme [benzylsuccinate synthase] utilizes toluene, and everything is packed very tightly around that molecule. So it’s not like it can just take anything — it’s very specific for that par-
ticular molecule."

**Biores-mediation and beyond**

This has larger implications for the practice of bioremediation, Funk says: "If you're going to be doing bioremediation, you're going to need many different kinds of enzymes that are capable of degrading all different kinds of substrates."

It’s not just in labs where microbes thrive on hydrocarbons. "Some microbes will grow abundantly near oil refineries, to the point that the oil companies are not happy about it because it's clogging up all of their pipes," Drennan says. "This actually gives weight to the idea that microbial bioremediation could work, because it's evidence that microbes can be very happy and take care of things in such an environment."

It’s also evidence that the discoveries concerning microbial structure that Drennan and Funk reveal in their paper could have more than one use. "Pipe erosion has been an issue because organisms reduce sulfate to hydrogen sulfide," Funk says, "which is a really nasty way to corrode pipes."

And pipe erosion in an oil refinery can only mean one thing: heightened probability of a spill.

With this issue in mind, Drennan and Funk acknowledge the irony that their structural discoveries may sooner be used for the inhibition of microbes than for fostering their growth. "I hope that this work doesn't just lead to an inhibitor that kills the organisms so they don’t corrode the pipes," Drennan says. "But if it prevents spills, that's good. You want the right amount of microbes cleaning up the environment, but not so much that they actually pollute it."

Whatever the immediate uses of their latest discovery, Drennan and Funk’s love affair with microbes is far from over. The DNA sequencing of microbes in particular presents an exciting frontier. "If you have these DNA sequences," Funk says, "you can turn out a profile of what the microbes are able to degrade in a particular spill situation, as well as what's been able to slip through because it doesn't have a degradation pathway. Sequence information can tell you a lot -- it can give you a much bigger picture about a whole community of organisms."

A bacterium that is the most common cause of pneumonia — a leading cause of death worldwide — can damage DNA in lung cells, a new study has shown.

Researchers from the Singapore-MIT Alliance for Research and Technology (SMART) demonstrated that hydrogen peroxide secreted by some strains of *Streptococcus pneumoniae* causes DNA in human lung cells to suffer double-strand breaks. Such breaks sever the DNA, creating broken ends that are highly toxic to cells, leading to cell suicide, or apoptosis.

“Secretion of hydrogen peroxide damages the DNA of lung cells, crippling the lungs’ defenses against invasion and making it easier for the bacteria to get into the bloodstream,” says Bevin Engelward, the paper’s senior author and a professor of biological engineering at MIT.

The discovery, she says, could lead to improved treatment for pneumonia patients by providing a means of measuring a person’s susceptibility to the disease. The study was led by Engelward, an expert in DNA damage and repair, and Vincent Chow, a professor and microbiologist at the National University of Singapore.

The study is published today in the *Proceedings of the National Academy of Sciences*. The lead author was Prashant Rai, a researcher in the infectious disease group at SMART.

“Hydrogen peroxide is commonly used as a disinfectant because of its ability to kill a wide range of microorganisms,” says Eric Rubin, a professor of immunology and infectious diseases at Harvard University who was not involved in the research. “[This study] turns this concept around: It is the microbe, *S. pneumoniae*, that is using hydrogen peroxide, this time to damage the host.”

In addition to Rai and Engelward, the research team included MIT collaborators Marcus Parrish, Ian J.J. Tay, and Shelley Ackerman; Na Li and Chow at SMART’s infectious disease group; and Fang He and Jimmy Kwang from Temasek Life Sciences Laboratory.

**Toxic breaks**

Physicians and researchers alike have long known that bacteria can infect people weakened by influenza — and that those infections can be fatal.

“In the 1918 flu pandemic, most deaths were caused by secondary bacterial pneumonia, especially infection with *S. pneumoniae*,” Chow says. “There is autopsy evidence to show that it wasn’t influenza that directly killed patients, but mortality was mainly due to the secondary bacterial infection that followed. That was what really motivated our lab to study *S. pneumoniae*: It’s clearly tied to flu pathogenicity. We wanted to investigate if *S. pneumoniae* and its products, such as hydrogen peroxide, could inflict dam-
Until now, however, DNA double-strand breaks were not among the harms thought to be caused by *S. pneumoniae*.

“There have been previous reports [of DNA damage] for certain bacteria, but nobody expects DNA damage to play a role in an acute infection like pneumonia,” Rai says.

The team used fluorescent dyes to locate DNA-repair foci, phosphorylated histone proteins that form at the site of DNA double-strand breaks and are thought to play a role in repairing DNA damage. After testing three strains of *S. pneumoniae*, the team found that the presence of the bacteria resulted in a significant increase in the frequency of double-strand breaks, and that this DNA damage caused apoptosis.

In their experiments, the amount of hydrogen peroxide and the amount of DNA damage produced by the bacteria both depended on the bacterial strain. One strain in particular caused a relatively high number of DNA double-strand breaks; this same strain also produced the most hydrogen peroxide.

The researchers then aimed to determine how significant DNA damage from hydrogen peroxide was in the actual disease. To do this, the researchers tested two strains of *S. pneumoniae* in mice, some of which were infected with the strain the team had found to produce the most hydrogen peroxide; the other was genetically engineered so that it could not produce hydrogen peroxide. These experiments demonstrated that bacteria that produced hydrogen peroxide more easily invaded the lungs and bloodstream.

“It is an important piece of work that extends our knowledge of how bacterial infection can cause lung injury,” says David Dockrell, a professor of infectious diseases at Sheffield University who was not involved in the research.

**Too much hydrogen peroxide**

The human body produces hydrogen peroxide at sites of inflammation: If the body senses an infection, it activates an innate inflammatory response that includes immune cells, such as macrophages and neutrophils. What they produce are reactive oxygen and nitrogen species, which includes an increase in hydrogen peroxide — really toxic chemicals meant to beat down the infective agent,” Engelward says.

“If the bacteria itself produces hydrogen peroxide, maybe it pushes past the threshold that the host can tolerate,” Rai adds.

Moreover, the inflammatory response might not work against hydrogen peroxide-producing bacteria. “*S. pneumoniae* strains that secrete hydrogen peroxide are predicted to be resistant to our body’s reactive oxygen species, used in an attempt to clear the infection, since the bacteria already tolerates its own reactive oxygen species,” Engelward says.

“The immune system’s ability to create reactive oxygen species may not be very helpful against certain strains of *S. pneumoniae*. It is possible that it might be hurting rather than helping,” Rai says.

**Screening people and bacteria**

The discovery that strains of *S. pneumoniae* cause DNA damage could open pathways to improved triage and treatment, based on the specific combination of patient and bacterial strain.

“It’s known that there is variability in DNA-repair capacity among people: Some people repair their DNA better than others,” Engelward says.

Combined with these latest research results, that suggests that a person with lower capacity for DNA repair might be more susceptible to certain types of pneumonia.

Engelward’s lab and that of Leona Samson, a professor of biology and biological engineering at MIT, have been working on technologies that can measure a person’s ability to repair DNA damage. Technologies already exist to determine which strain of pneumonia a person is infected with. But such technologies, paired with the ability to measure a person’s DNA-repair capacity, could one day allow hospitals to determine, early on, just how bad a particular pneumonia infection will be for a particular patient. Being able to predict who is most susceptible to fatal pneumonia could ultimately save lives.

Getting Political: Friends of the Malden River Engages Elected Officials to Help Clean Polluted Waterways

Adapted from an article by Karen Buck, https://maldenriver.wordpress.com/
Forward and Afterward by Kathleen M. Vandiver, MIT CEHS COE²C Director

Forward: The MIT CEHS COE²C Director, Kathleen Vandiver, has been a hardworking member of the community group Friends of the Malden River (FoMR) for the past two years. When FoMR decided to file a Massachusetts Public Involvement Plan (PIP) against a Honeywell Inc. property, the group needed to take their game to the next level. On Vandiver’s recommendation, Toxics Action Center, an advocacy organization, was invited to lead FoMR’s planning sessions for this public hearing. One of the goals we wanted to achieve was to draw local politicians to our cause.

The Public Hearing: Held on June 4, 2015 where over 60 residents and City Officials of the Medford, Malden and Everett townships came to show their support for the Malden River. The FoMR petitioned Honeywell Inc. to inform the public of their corporate history (through Allied Chemical and Dye) with the river, their recent clean-up work, and their future intentions of the 378 Commercial Street property in Malden.

The Friends of the Malden River, a grassroots community group, utilized Massachusetts Department of Environmental Protection laws in order to create transparency in regards to toxic chemical monitoring on a Honeywell Inc. property. This location has been dubbed as one of the most contaminated sites on the Malden River. Honeywell, Inc. is obligated by the law to publicly present their past, present and future plans to monitor this polluted site.

The Malden River was used heavily by industry in the late 1800s through the mid-1960s. Allied Chemical and Dye (who purchased Honeywell, Inc. in 1999 and adopted the incorporated name) manufactured roofing and coal tar materials. The production of these materials also produced many toxic chemicals and heavy metals. Different toxic by-products have been detected in the soil, including extremely high levels of naphthalene. Long term exposure has been reported to cause cataracts and damage to the retina. EPA has classified naphthalene as a possible human carcinogen (epa.gov).

During a mandated 2008 cleanup, only 11,000 cubic yards of coal tar impacted soil was removed from the Little Creek bank which was re-vegetated with native plants. On this nine acre site, there is an 115,000 sq. ft. building and an asphalt parking lot that covers more of the toxic soil. The less feasible alternative of removing a large building resulted in a temporary release that requires testing of the monitoring wells once every five years. The FoMR’s main concern is whether the toxins are still leaching into the Malden River. One of the greatest questions is whether Honeywell, Inc. will explore that possibility and remediate if necessary. The Friend’s quest is for a complete cleanup and total remediation for a cleaner river. The ultimate goal is for unlimited use.

The Malden High School crew team came to the Public Hearing where their presence represented the youths affected by historical misuse of our natural resources. Terrica Dang, one of the captains, describes the team’s experiences on the river. “Whenever we talk to other townspeople about crew and rowing on the river, we always get mixed reactions,” Dang laments. “Whenever other crew teams come down and they try to do a coxswain toss (throwing a coxswain into the river) after a victory, we always have to tell them not to.” Dang continues, “The one thing I regret most about the river is that I am unable to dunk my hands in the water like I do with other rivers. But, I am grateful that the river is here so it can give urban cities like Malden, Somerville, Everett and Medford a place to have high school kids row and take on a sport that isn’t available everywhere.” Dang’s story is one of the many reasons why the Friends of the Malden River want to speak up for the river, since it has lost its voice centuries ago.

Afterward: The June 4th Public Hearing garnered attention in the political arena. First with a follow up meeting in July with two State House representatives, Rep. Stephen Ultrino (Malden) and Rep. Joseph McGonagle Jr. (Everett). The representatives were concerned about the health of the students rowing on the river. They offered to obtain State funding for a human health risk assessment, and together agreed to meet quarterly for strategic planning purposes. Secondly, FoMR members, Hue Holley and Teresa Bello, were instrumental in getting “The Community Preservation Act” passed by voters in Malden, MA. Funds from this Act could potentially lead to a river clean-up as well. And lastly, U.S. Congressman Michael Capuano, a longtime advocate for clean water, gave the keynote address on October 19, 2015 at the annual meeting of the Mystic River Watershed Association of which the Malden is a part. Congressman Capuano mentioned local watershed associations play a very important role, convening stakeholders to join conversations and focus on the river. He closed by thanking the association for maintaining the public’s attention on the health of our rivers.
Introduction
Maine is home to five federally recognized tribes. Each tribe has an environmental science office with a professional team that works closely with the tribe’s elders to maintain the nation’s natural resources and plan for the future. In this endeavor, the five tribes in Maine frequently collaborate with each other and with the staff at EPA Region 1. This article summarizes the MIT CEHS COE²C’s growing engagement with the Native American community after listening to their environmental health concerns raised earlier in previous conversations. The three projects demonstrate our responsiveness to community needs, primarily focused on effective teaching tools for youth groups and assistance in managing instrumentation and analyzing environmental air quality data.

Contributions to the New England EPA Tribal Summit 2015 held on October 2015
Over the past two years, the MIT CEHS COE²C Director, Kathleen Vandiver, has become more familiar with the New England’s tribal environmental issues through monthly teleconferences with the Regional Tribal Operations Committee (RTOC) in EPA Region 1. These interactions led to an invitation to participate in the New England EPA Tribal Environmental Summit entitled “Preparing the Next Generation of Tribal Stewards for Emerging Environmental Challenges” held in October 2015 in Presque Isle, Maine. The Summit was hosted by the Aroostook Band of Micmacs with tribal leaders from all over New England and by EPA Region 1 senior leadership. The MIT CEHS faculty member, Professor Noelle Selin, presented a talk on “Global Mercury Modeling and Implications for Local Communities.” It was the first time many tribes had heard a mercury expert provide concrete data showing that it will be many generations before the tribes in New England can safely return to their traditional fish diet for sustenance. In addition, MIT COE²C’s materials “A Learning Table for all Ages: Understanding Air” was presented at the conference. Vandiver was assisted by two MIT students as they led high school youths through activities that explained the chemistry behind climate change and air pollution.

Collaborations with the Innovative Wabanaki Youth Science Program (WaYS)
The Wabanaki Youth Science program is an educational program that integrates modern technology, science, and Traditional Ecological Knowledge (TEK). This program, which began in 2013, was created by Professor Darren Ranco at University of Maine, Tish Carr, a natural resources professional, and Barry Dana, a WaYS cultural knowledge keeper who is a Penobscot community elder and former tribal chief. This program offers three features: a week-long summer camp; a high school internship with a tribal environmental program; and an after-school program with TEK for middle schoolers at a local teen center. This program helps youth persist in studying science as well as to continue their legacy as first stewards of the earth. Vandiver led two training sessions for WaYS educators in the fall of 2015, one in South Portland, Maine and another in Orono, Maine. The MIT CEHS donated two hands-on classroom sets for two different lessons. One of the sets uses model fish with chromosomes that animate the relationship between genes and traits. The second set teaches chemistry with bricks as atoms to illustrate how atoms behave in chemical reactions. The reactions can lead to larger insights such as how carbon cycles in nature and the role of forests in sequestering carbon.

Co-sponsoring Teacher Professional Development Workshops with Maine Indian Education (MIE)
On August 2015, Vandiver, Nancy Dalrymple, and John Essigmann (MIT CEHS Center Director) met with Maine Indian Education (MIE) leaders, Beth Clifford and Dana Mitchell, at the Wabanaki Culture Center on the banks of St. Croix River. After Vandiver presented the COE²C materials, she was invited by Beth Clifford to lead two professional development workshops for their teachers. Vandiver returned to Calais, ME again in mid-November 2015 to present the two workshops using the CEHS donated MIT Edgerton Center Molecule Set. One teacher was eager to share the set with his class the next day!
MIT faculty and U.S. Rep. Joe Kennedy III met at the Media Lab on Sept. 3 for an event that highlighted technology’s potential to improve the quality of and access to STEM education. Called “Scaling STEM,” the event featured opening remarks by MIT President L. Rafael Reif, followed by presentations from Kennedy, Dean of Digital Learning Sanjay E. Sarma, and four professors from MIT.

Kennedy said that “MIT is leading the way” in reaching underserved parts of the population when it comes to STEM.

In a panel discussion, Mitchel Resnick, who leads the Lifelong Kindergarten lab, discussed one of his lab’s projects, Scratch, which K-12 students have used to learn programming for the past eight years.

Angela Belcher, a materials science and biological engineering professor, discussed her efforts to teach STEM to students at a young age. She shared her belief that elementary students should be taught about chemical reactions, solar cells, and other topics that are usually left to high school or college.

Eric Klopfer, an MIT professor and director of the Education Arcade, offered a compelling way for younger students to become engaged in STEM material through video games. One of his lab’s projects is Radix, which combines the excitement of a massive multiplayer online game with the educational value of science exercises.

The Scaling STEM event comes at a time when MIT is reconsidering the education that it offers to its own students, as well as beyond, given the development of digital tools and online courses. In August 2014, an Institute-wide task force on the topic proposed a more modular and flexible future for education at MIT.

http://tech.mit.edu/V135/N21/stem.html

COE²C Director Vandiver Participated in the Beijing Science Festival

"Understanding Air: Teaching Key Concepts about Climate Change and Air Pollution in Beijing"

MIT CEHS COE²C Outreach Director, Kathleen Vandiver, was invited by the Beijing Association of Science & Technology (BAST) to bring MIT’s hands-on science teaching materials to the Beijing Science Festival held in September 2015. Her materials taught the public about climate change and air pollution. To prepare the booth volunteers for the Festival, Vandiver led a training workshop last June for 80 bilingual Chinese students who visited the MIT campus (See COE²C Events: June 26, 2015). Additional students were trained on site.

During the six-day festival at our MIT CEHS booth, the public was invited to build models of molecules using bricks to represent individual atoms when the combustion reaction was modeled, the greenhouse gas carbon dioxide was produced. Visitors also modeled an incomplete combustion reaction that produces pollutants such as carbon (soot) and carbon monoxide. Burning fuel such as coal can cause increases in the levels of lung-damaging molecules such as SO₂, NO₂, and O₃, and can add more particulate matter into the air as well. This combination of unhealthy molecules and particulates can be found in many urban areas around the world. By helping the general public understand air better, we hope that more people will be motivated to do their part and work towards improving the world’s air quality.
Chemistry, Toxicology and Biological Engineering at MIT, who led the current research.

“They found the lesions were very persistent in DNA, meaning we don’t have a repair system to take them out,” Essigmann says. “In our field lesions that are persistent, if they are also mutagenic, are the kind of lesions that would initiate cancer,” he adds.

DNA sequencing of a developing gastrointestinal tumor revealed two types of mutation: cytosine (C) bases changing to thymine (T) bases, and adenine (A) bases changing to guanine (G) bases. Since 5ClC had not yet been studied as a potentially carcinogenic mutagen, the researchers decided to investigate the lesion further, in a bid to uncover if it is indeed mutagenic.

Using a technique previously developed in Essigmann’s laboratory, the researchers first placed the 5ClC lesion at a specific site within the genome of a bacterial virus. They then replicated the virus within the cell.

The researchers found that, rather than always pairing with a guanine base as a cytosine would, the 5ClC instead paired with an adenine base around 5 percent of the time — a medically relevant mutation frequency, according to Essigmann.

Damaged DNA

The findings suggest that the immune system, when triggered by infection, fires hypochlorous acid at the site, damaging cytosines in the DNA of the surrounding healthy tissue. This damage causes some of the cytosines to become 5ClC.

In addition, the researchers hypothesize that the hypochlorous acid also damages cytosines in the nucleotide pool, which cells use as the reservoir of nucleotides that will become part of the DNA of replicating cells, Essigmann says. “So 5ClC forms first in genomic DNA, and secondly it can form in the nucleotide pool, meaning the nucleotides in the pool are mutagenic in themselves,” he explains. “This scenario would best explain the work of James Fox and his MIT colleagues on gastrointestinal cancer.”

To confirm that 5ClC is mutagenic in human DNA, the researchers replicated the genome containing the lesion with a variety of different types of polymerase, the enzyme that assembles DNA, including human polymerases. “In all cases we found that 5ClC is mutagenic, and causes the same kind of mutations seen within cells,” Fedele says. “That gave us confidence that this phenomenon would in fact happen in human cells containing high levels of 5ClC.”

What’s more, the C-to-T mutation characteristic of 5ClC is extremely common, and is present in more than 50 percent of mutagenic “signatures,” or patterns of DNA mutations, associated with cancerous tumors. “We believe that in the context of inflammation-induced damage of DNA, many of these C-to-T mutations may be caused by 5ClC, possibly in correlation with other types of mutations as part of these mutational signatures,” Fedele says.