Oxygen's radical role in cancer and aging

For most animals, oxygen is the breath of life. But depending on the chemical company it keeps, oxygen can just as easily become a damaging radical — fostering disease or shortening the life of those it touches. Several new studies now refine this picture of oxygen's toxic alter ego.

One provides further support for the idea that oxidative stress plays a causal role in aging. Two others find new evidence that oxidant molecules not only might promote the development of cancer, but also foster its spread.

In the Dec. 6 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (PNAS), Rajindar S. Sohal and Sanjiv Agarwal of Southern Methodist University in Dallas correlate a housefly's lifetime accumulation of oxidant-induced DNA damage with life span. Whether DNA's oxidation occurred as a result of physical activity, exposure to ionizing radiation, or breathing in pure oxygen instead of normal air, the result was the same: The higher the buildup of oxidized DNA, the less time a fly lived.

Moreover, the two researchers observed, the rate of DNA oxidation — and, presumably, aging — accelerated with time. Sohal now believes that this traces to something his group has observed in a series of earlier studies: The effectiveness of the animal's antioxidant defenses declines over time — while internal generation of damaging, free-radical oxidants per unit of physical activity, radiation, or respiration increases with age.

All the DNA proved susceptible to the modification studied — oxidation of a particular DNA nucleoside. Such changes "can lead to disrepair or a mutation," Sohal explains. But DNA in a fly's mitochondria — those structures that power cellular activities — proved 3.3 times as likely to oxidize as nuclear DNA.

Within the fly's body, "mitochondria are the main source of radicals," Sohal notes. But when oxidants damage mitochondrial membranes directly, he says, or perhaps alter membrane function through DNA changes, then the mitochondria's output of radicals can climb even higher. So it appears "that mitochondria play an important role in aging by being both a primary source of radicals and primary site of [radical] damage," Sohal told SCIENCE NEWS.

Because mammals are susceptible to the same oxidative changes witnessed in flies, he points out, many biologists are coming to suspect that a similar relationship between oxidation and aging may play out in humans.

Other studies have already firmly established a tie between oxidative damage and chronic illness — from cancer to heart disease. In the same PNAS, Rayudu Gopalakrishna and his colleagues at the University of Southern California School of Medicine in Los Angeles report on mechanisms behind one such link: cancer and the tar deposited in the lungs by cigarette smoke.

The researchers showed that injected tumor cells were more effective at spawning cancerous growths in the lungs of those mice treated first with cigarette-smoke tars. In separate cell studies, the USC team went on to show that catechol and hydroquinone — two water-soluble chemicals that can leach out of smoke's tars — increased the invasiveness of tumor cells by spurring the production of oxidants. Moreover, they traced these invasiveness changes to the oxidants' effects on the regulation of calcium and protein kinase C (PKC), a ubiquitous cell enzyme.

Other studies have linked cancer-cell invasiveness to changes in calcium and PKC signaling, notes Lance A. Liotta of the National Cancer Institute in Bethesda, Md. Though cigarette smoke had not previously been linked to these cell-signaling pathways, Liotta does "not find the idea all that surprising." But the new USC findings do suggest that "continual cigarette smoking might influence the acquisition of invasive capacity by tumor cells," Liotta says — turning a cancer potentially lethal.

"Gopalakrishna's work dovetails nicely with ours," says William A. Pryor of Louisiana State University in Baton Rouge. His team has shown that the same water-soluble tar extracts can bind to DNA and "nick" it — snip through one of the molecule's two linked strands. Nor does one have to smoke to experience such an effect. A paper by Pryor's team in the October ENVIRONMENTAL HEALTH PERSPECTIVES notes that cells exposed to environmental tobacco smoke generate the same DNA-nicking oxidants as those exposed to mainstream cigarette smoke.

Moreover, Pryor says, "we've shown that the components of cigarette smoke that nick DNA do it in a way that's resistant to repair" and prone "to mutation or carcinogenesis." — *J. Raloff*

Designing proteins to block cancer genes

It's hard to find a gene that causes tumor cells to grow when turned on and inhibits growth when turned off. It's even harder to figure out how to switch off such oncogenes.

Going after this problem from the viewpoint of protein engineering, Aaron Klug, a molecular biologist at the Medical Research Council laboratories in Cambridge, England, and his colleagues report designing and synthesizing a protein that can disable an oncogene in mouse cells grown in the laboratory. The 90-amino-acid peptide binds to a DNA target in a gene associated with leukemia. Their report appears in the Dec. 15 NATURE.

"Our goal in this experiment is proof of principle," Klug says. "We wanted to show that it's possible to make a protein that can act on a specific oncogenic sequence of chromosomal DNA, discriminating it from similar sequences."

Klug's peptide uses three zinc fingers, each a unit of 30 amino acids that can locate and grip a DNA sequence of three base pairs. Building on work reported in the Nov. 8 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, Klug linked three zinc fingers, thus enabling the peptide to select a DNA target nine base pairs long. Klug chose the oncogene known as bcr-abl. In humans, this gene can lead to a truncated chromosome 22, which has been associated with leukemia.

Klug used two types of cancer-prone, or oncogenic, mouse cells for his experiment. One type provided a target for the customized peptide; the other, with a related but slightly different oncogene, served as a control. Ordinarily, both cell types require the growth factor interleukin-3 to survive. Yet with their oncogenes turned on, they reproduce without the growth factor.

After exposing both types of cells to the peptide, he found that the controls continued to reproduce without growth factor — indicating that their oncogenes remained on. In the other cell type, whose oncogene served as the peptide's target, the cells died without growth factor.

This result suggests, says Klug, that the peptide bound to and blocked the oncogene in the target cell line but not in the control cells.

"This is an excellent experiment," says James A. Wells, a molecular biologist at Genentech, a biotechnology firm in San Francisco. "If zinc fingers can enter cells, then perhaps they can be used to regulate specific genes. It's an important step."

Klug cautions that "this is not a cure for cancer. We've only used mouse cells, not human cells. And we have no means at the moment for delivering an oncogenic blocker" to a tumor. However, he stresses that these results show the feasibility of making peptides from modules that can block very specific portions of DNA in live cells without disturbing closely related gene sequences.

"This technique has many possible uses, and we've only explored one in detail. Yet the fact that we've blocked an oncogene in a mouse cell line is a graphic demonstration of this technique's potential power." — *R. Lipkin*