Oxygen plays role in cancer aggressiveness

Oxygen-starved cancer cells from mice increase their deadliness when flooded with oxygen in the lab and then injected into healthy mice, according to a new study. The finding raises safety questions about proposed anticancer treatments that aim to kill tumors by shutting off their blood supply.

Previous research has shown that placing cultured cancer cells in a low-oxygen environment and then reoxygenating them boosts their ability to spread and to survive harsh treatment with anticancer drugs. Those studies hinted that tumor cells robbed of oxygen in the body might also develop aggressive qualities when reoxygenated.

Now, a Canadian research team has tested that idea in mice, using two skin cancers and a connective tissue cancer. They found that tumor cells located far from blood vessels — and thus from the oxygen supply — show a greater tendency to metastasize to distant parts of the body after reoxygenation than tumor cells situated close to the blood supply.

Richard P. Hill and S.D. Young of the Ontario Cancer Institute in Toronto injected a fluorescent dye into the blood of cancer-afflicted mice and removed tumor tissue. They sorted the cells by the amount of oxygen each received in the body: Cells close to the blood supply glowed more than distant oneş because they picked up more dye. Hill and Young then exposed all the cancer cells to oxygen for up to 10 days and injected the cells into the tail veins of healthy mice. After 20 days, the researchers counted the number of lung tumors that had developed in these mice, a measure of how aggressively the injected cells proliferated and migrated to distant body sites.

Hill and Young found that the tumor cells originally derived from the most oxygen-starved sites *in vivo* showed double the metastatic efficiency of cells from well-oxygenated regions. That finding, detailed in the March 7 Journal of the National Cancer Institute, prompts questions about experimental attempts to kill tumor cells by interfering with their blood supply. Last year, for example, a New Zealand research team reported killing cancer cells in mice by using an experimental anticancer drug, flavone acetic acid, to restrict blood flow to the tumor.

The success of that work led to hopes that a similar treatment might benefit human cancer patients. But the Canadian study suggests such an approach could backfire if some cancer cells survived the drug assault. If Hill and Young's findings are correct, says J. Martin Brown of the Stanford University School of Medicine, any remaining oxygen-deprived cells might show a heightened ability to seed new cancer growths when their blood supply is restored. Brown wrote an editorial accompanying the Canadian research report.

The Canadian team's results seem to contradict earlier reports that oxygen-deprived tumor cells show extra resistance to standard chemotherapy. Hill and Young found that oxygen-deprived tumor cells removed from mice and reoxygenated were just as sensitive to the anticancer drugs methotrexate and doxorubicin as well-oxygenated tumor cells. However, Hill told Science News he won't rule out the notion that oxygen-deprived tumor cells are more drug-resistant. The methods used in his study, he says, may not have been able to detect very small numbers of drug-resistant cancer cells that could nevertheless spread malignancy through the body.

Scientists don't know why the oxygen deprivation/reoxygenation sequence seems to produce such aggressive tumor cells. Hill speculates that it increases expression of genes that regulate the cells' ability to proliferate. The new study revealed that the most aggressive cancer cells — those from the poorly oxygenated sites — contained "excess" DNA in comparison with tumor cells from well-oxygenated areas, he notes. In future research, Hill says, the team will seek a connection between this overabundance of DNA and specific genes that may be involved in cancer spread. *— K.A. Fackelmann*

Lakes may slow pollutant removal from air

Surprisingly high levels of potentially toxic air pollutants return to the air from the waters into which they have fallen, a new study indicates. This finding helps solve the mystery of why polychlorinated biphenyl (PCB) levels over the Great Lakes haven't diminished since the 1977 ban on their production. It also suggests that lakes and other bodies of water may facilitate the migration of industrial air pollutants toward polar climes from the relatively warm areas where they're made and used.

Water-insoluble air pollutants such as PCBs and polycyclic aromatic hydrocarbons (PAHs) generally settle out of the atmosphere within days of their release. For years, scientists assumed these contaminants took a quick, one-way route into oblivion no matter where they fell. Those falling on land do tend to get buried in soil or washed into local streams with rain soon afterward. Similarly, those deposited in bodies of water were thought to attach to large particles, such as suspended bits of soil, and to settle out as sediment.

But the watery fate of these chemicals may prove more complicated, researchers now report.

In the 1950s, '60s and '70s, the atmosphere clearly served as the leading source of chemical contamination to the upper Great Lakes, notes Joel E. Baker, a chemist at the University of Maryland's Chesapeake Biological Laboratory in Solomons. That's not the case today, his new data suggest.

While at the University of Minnesota in Minneapolis, he and Steven J. Eisenreich analyzed air and water sampled from a number of sites in eastern and central Lake Superior for 35 different PCBs and 14 PAHs, including the carcinogens benz[a]-anthracene, phenanthrene, pyrene, chrysene and benzo[a]pyrene.

In the fall, winter and spring, they found, air appears to remain the net source of these pollutants, depositing them in the lake. In the summer months, however, the lake becomes the net source, recycling the contaminants back into the air through a process called revolatilizaton. The lake's summertime release appears to equal the pollutant levels deposited into the lake from the air during the entire rest of the year, the researchers say. Baker and Eisenreich report their findings in the March Environmental Science and Technology.

Though scientists had some hints that pollutants might return to the air from lakes, Baker says, "until we did this study, the magnitude of potential volatilization was not really appreciated."

Driven largely by temperature, the revolatilization of pollutants from the water into the air should occur more frequently in warmer climates than in cold ones, Baker explains. Each time the pollutants return to the air, they can waft farther from their initial source. But when they drift into colder regions, the less efficient revolatilization from surface waters should result in a proportionately higher rate of permanent pollutant fallout, Baker says. Indeed, this mechanism might help explain the high levels of PCBs and organochlorine pesticides found in the Arctic, far from their release sites.

If this pollutant recycling also occurs in oceans, "then the oceans could perhaps account for the level of contamination that we're seeing in Arctic," says Dennis J. Gregor, a geochemist with Environment Canada in Burlington, Ontario. However, Gregor says, the apparent lack of chemical transformation or "aging" he sees in the Arctic PCBs and pesticides suggests they were not recycled through water but instead were carried directly from their sources, probably in Eurasia. For this reason, he thinks the "most worrisome" aspect of the new findings is the implication that a disproportionate share of these contaminants will stay in the Arctic, where cold weather hinders natural pollutant degradation. *— J. Raloff*