Carbon monoxide can help shrink tumors and amplify effectiveness of chemotherapy

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In recent years, research has suggested that carbon monoxide, the highly toxic gas emitted from auto exhausts and faulty heating systems, can be used to treat certain inflammatory medical conditions. Now a study led by a research team at Beth Israel Deaconess Medical Center (BIDMC) shows for the first time that carbon monoxide may also have a role to play in treating cancer.

The surprising new findings, described in the December issue of the journal *Cancer Research*, show that in cell culture and animal models carbon monoxide (CO) can both prevent tumor growth in prostate and lung cancers and can amplify the effectiveness of chemotherapy 1,000-fold – while sparing noncancerous tissue from chemo's sometimes debilitating side effects.

"We found that in small, carefully controlled doses, CO not only mimicked the effects of chemotherapy agents by blocking proliferation of cancer cells, but also amplified the toxic effects of the chemotherapy drugs doxorubicin and camptothecin to accelerate cancer cell death," says senior author Leo Otterbein, PhD, an investigator in the Transplant Institute in BIDMC's Department of Surgery and Associate Professor of Surgery at Harvard Medical School. "Importantly and rather unique is that CO also helped to protect normal tissue from chemotherapy, which is an unfortunate side effect of the treatments."

The new discovery appears to hinge on CO's ability to switch the metabolic state of cancer cells so that tumors essentially work

themselves to death. "There are fundamental differences in the metabolism of normal cells and cancer cells," explains Otterbein. "Cancer cells are able to alter their metabolism in processing sugars and other energy sources, which enable them to rapidly proliferate and spread. This shift in metabolism is known as the Warburg Effect. Our findings indicate that CO essentially induces an 'anti-Warburg' effect, rapidly fueling cancer cell bioenergetics by compelling the cancer cell to increase respiration, which ultimately results in metabolic exhaustion."

The body naturally generates CO under stress through the increased expression of the gene heme oxygenase-1 (HO-1 Hmox1), a cytoprotective stress response gene that generates CO as it catabolizes heme, an essential component of many proteins such as hemoglobin. The increase in HO-1 has been shown to occur under numerous and diverse stressors, such as inflammation, trauma and even tissue repair. Tumors, however, are often absent this capability because HO has become inactive and unable to generate sufficient levels of CO. In this new paper, Otterbein and first author Barbara Wegiel, PhD, also an investigator in BIDMC's Transplant Institute, wanted to find out if a tumor's inability to produce CO naturally was what was fueling cancer growth.

"If A plus B equals C, then, we reasoned, if you administered carbon monoxide to tumors, you would reestablish a tumor cell's ability to regulate its cell growth, and so, too, slow that growth," says Otterbein.

The authors first conducted a detailed analysis of more than 500 tumor samples from prostate cancer patients. "Through these biopsies, we confirmed expression of HO-1," explains Wegiel, who is also an Assistant Professor of Surgery at HMS. "But we found that HO-1 in the tumor was simply not active. It was not producing sufficient amounts of CO, and we thought this was contributing to altered cell growth and malignancy."

This finding led to their hypothesis that HO-1, through its ability to generate CO, was regulating the growth of cancer cells, a discovery that had been observed and well described in other cell types. To test this hypothesis, mice with established tumors were started on a regimen of inhaled CO of one hour per day at a safe, low concentration, equal to that approved for use in humans in ongoing clinical trials. Tumor size was measured daily over four to six weeks. In the cancer cell CULTURES, metabolic activity in the mitochondria – the cells' energy-generating organelle— were measured using biochemical markers as well as imaging techniques.

"We found that exposure to CO sensitized the prostate cancer cells—but not the normal cells—to chemotherapy," explains Otterbein. "CO targeted mitochondria activity in cancer cells as evidenced by higher oxygen consumption, free radical generation and, ultimately, mitochondrial collapse.

"Collectively, our findings indicated that CO induces an anti-Warburg effect by rapidly fueling cancer cell bioenergetics, ultimately resulting in metabolic exhaustion," he adds. Importantly, CO protected normal cells from DNA damage generated by cytotoxic agents, in part by reducing oxygen consumption and eliciting a hibernation-like state in these cells. "Essentially, these normal cells entered growth arrest and slowed their metabolic rate, in marked contrast to the cancer cells, which continued to consume oxygen at a rate that ultimately led to their demise."

While the authors note that more research will be needed to confirm these findings, they provide a promising new direction for cancer treatment.

"Chemotherapy remains the first-line therapy for many types of cancer, including breast and lung cancers," notes study coauthor and BIDMC Chief Academic Officer Vikas Sukhatme, MD, PhD. "But

chemotherapy's debilitating side effects and limited effectiveness are well known. This new finding opens up the possibility of new therapeutic interventions that take advantage of powerful chemotherapy drugs, perhaps making them even more potent while simultaneously limiting their terrible side effects and damage to normal cells and tissues. There are ongoing innovative methodologies being designed and tested to deliver CO directly to the tumor site, which might obviate the need for additional drugs. Indeed, small molecules are being designed that can carry CO as a cargo and deliver it in a tissue-specific manner."

Provided by Beth Israel Deaconess Medical Center