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BP - Cancer and cell oxygenation

https://www.sciencenews.org/article/dose-extra-oxygen-revs-cancer-fighting-immune-cells

Dose of extra oxygen revs up cancer-fighting immune cells

Lung and breast tumors in mice shrank with treatment, study shows

By Tina Hesman Saey 2:00pm, March 4, 2015

Boosting oxygen in the air helped mice with cancer battle lung and breast tumors.

Normal air contains 21 percent oxygen. Raising oxygen concentrations to 60 percent energized immune cells to shrink tumors in mice, researchers report in the March 4 Science Translational Medicine. About 40 percent of cancer-ridden mice put in an oxygen-rich environment survived 60 days or more. In contrast, mice that breathed normal air after getting an injection of lung-cancer cells died within about 30 days, say Stephen Hatfield of Northeastern University in Boston and colleagues.

Tumors grow rapidly as they suck up all the oxygen around them. Low oxygen causes tumors to release a chemical called adenosine, which makes immune cells sluggish and promotes tumor growth. Boosting oxygen counteracts adenosine and perks up immune cells called T cells and natural killer cells that shrink tumors, the researchers found.

A little extra oxygen may boost the effectiveness of immune therapies already being given to cancer patients, the researchers say. Too much oxygen can be toxic, though. And previous studies of people and animals have produced mixed results about the relationship between oxygen and cancer (SN: 2/7/15, p.6).

Citations

S.M. Hatfield et al. Immunological mechanisms of the antitumor effects of supplemental oxygenation. Science Translational Medicine. Vol. 7, March 4, 2015, p. 277ra30. doi: 10.1126/scitranslmed.aaa1260.

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Wim Hoff – called the Iceman because he can stay in ice water for 2 hours w/o suffering any damage – discovered/uses/teaches a breathing technique that so greatly boosts immune system and other functions, he has effectively worked with late stage cancer patients and been rigorously studied by science:

https://www.google.com/?gws_rd=ssl#q=the+superhuman+world+of+the+iceman

“A new study finds that giving high-dose oxygen may help efforts to stimulate the immune system against tumors. The study's only been done in mice and hasn't been shown safe in people yet — but it does open some possibilities, the researchers report in the journal Science Translational Medicine.

"This is exciting work," said Susanna Greer, director of clinical research and immunology for the American Cancer Society. "This is the kind of data that definitely makes you catch your breath a little bit."

Sitkovsky and colleagues looked at one particular property of tumors. They can live without much oxygen, in what are known as hypoxic environments.

"Since the root of all problems is the lack of oxygen in tumors, a simple solution is to give tumors more oxygen," Sitkovsky told NBC News.

This approach has been tried in many different ways and so far it hasn't worked. It's been such a failure that the American Cancer Society has a specific and detailed explanation.

"Available scientific evidence does not support claims that putting oxygen-releasing chemicals into a person's body is effective in treating cancer," the organization says. "Some types of oxygen treatment may even be dangerous; there have been reports of serious illness and death from hydrogen peroxide. Ozone is a strong oxidant that can damage cells, and has also caused deaths."

Sitkovsky's team wanted to try a non-toxic approach, giving a 60 percent oxygen mix — similar to what a patient gets in the hospital through an oxygen mask.

He found an important missing element in oxygen therapy — an immune response.

"If you give the oxygen and there are no tumor killer cells, then nothing happens to the tumor," he said. "Nobody understood that before. You must have killer cells. This is why oxygen until now was not successful in cancer," he added.

http://www.nbcnews.com/health/health-news/could-oxygen-make-cancer-therapy-work-better-n317446

http://www.medicaldaily.com/breathing-extra-oxygen-shows-promise-fighting-cancer-and-boosting-immune-system-will-324646

The idea seems simple, almost too simple — breathing in extra oxygen may boost immune cells in battling cancer. That's what Michail Sitkovsky, an immunophysiology researcher at Northeastern University, and his team have posited in a new study: that supplemental oxygen treatment could awaken "sleepy" cells in the body that are capable of fighting tumors.

The study makes bold claims, noting that it may make a dramatic improvement in cancer treatment — despite the fact that it was only completed in a mouse model. The researchers found that breathing in 40-60 percent oxygen compared to the 21 percent air provides could help weaken immunosuppression and fight the development in tumors by releasing T-lymphocytes.

"Breathing supplemental oxygen opens up the gates of the tumor fortress and wakes up 'sleepy anti-tumor cells, enabling these soldiers to enter the fortress and destroy it," Sitkovsky said. "However, if anti-tumor immune cells are not present, oxygen will have no impact."

Sitkovsky has been analyzing the effects of extra oxygen on cancer-fighting cells for decades now…

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http://mosao2.org/Article%20-%20Medicine/cancer_Otto_Warburg_00.pdf

On the Origin of Cancer Cells Author(s): Otto Warburg Source: Science, New Series, Vol. 123, No. 3191, (Feb. 24, 1956), pp. 309-314 Published by: American Association for the Advancement of Science Stable URL: http://www.jstor.org/stable/1750066

The first notable experimental induction of cancer by oxygen deficiency was described by Goldblatt and Cameron (3), who exposed heart fibroblasts in tissue culture to intermittent oxygen deficiency for long periods and finally obtained transplantable cancer cells, whereas in the control cultures that were maintained without oxygen deficiency, no cancer cells resulted. Clinical experiences along these lines are innumerable…

The mysterious latency period of the production of cancer is, therefore, nothing more than the time in which the fermentation increases after a damaging of the respiration.

…The era in which the fermentation of the cancer cells or its importance could be disputed is over, and no one today can doubt that we understand the origin of cancer cells if we know how their large fermentation originates, or, to express it more fully, if we know, how the damaged respiration and the excessive fermentation of the cancer cells originate.

We need to know no more of respiration and fermentation here than that they are energy-producing reactions and that they synthesize the energy-rich adenosine triphosphate, through which the energy of respiration and fermentation is then made available for life… This, converted to energy equivalents, means that the cancer cells can obtain approximately the same amount of energy from fermentation as from respiration, whereas the normal body cells obtain much more energy from respiration than from fermentation... Of importance for the considerations that follow are only the two stable independent metabolic processes, respiration and anaerobic fermentation-respiration, which is measured by the oxygen consumption of cells that are saturated with oxygen, and fermentation, which is measured by the formation of lactic acid in the absence of oxygen.

Injuring of Respiration

Since the respiration of all cancer cells is damaged, our first question is, How can the respiration of body cells be injured? …One method for the destruction of the respiration of body cells is removal of oxygen…Another method for destroying respiration is to use respiratory poisons. From the standpoint of energy, this method comes to the same result as the first method. No matter whether oxygen is withdrawn from the cell or whether the oxygen is prevented from reacting by a poison, the result is the same in both cases-namely, impairment of respiration from lack of energy. I may mention a few respiratory poi-sons. A strong, specific respiratory poi-son is arsenious acid, which, as every clinician knows, may produce cancer. Hydrogen sulfide and many of its derivatives are also strong, specific respiratory poisons. We know today that certain hydrogen sulfide derivatives, thiourea and thioacetamide, with which citrus fruit juices have been preserved in recent times, induce cancer of the liver and gall bladder in rats.

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http://cancerres.aacrjournals.org/content/49/23/6449.short

Blood Flow, Oxygen and Nutrient Supply, and Metabolic Microenvironment of Human Tumors: A Review[1]

1. **Peter Vaupel[2], Friedrich Kallinowski, and Paul Okunieff**

Abstract

The objective of this review article is to summarize current knowledge of blood flow and perfusion-related parameters, which usually go hand in hand and in turn define the cellular metabolic microenvironment of human malignancies. A compilation of available data from the literature on blood flow, oxygen and nutrient supply, and tissue oxygen and pH distribution in human tumors is presented. Whenever possible, data obtained for human tumors are compared with the respective parameters in normal tissues, isotransplanted or spontaneous rodent tumors, and xenografted human tumors. Although data on human tumors *in situ* are scarce and there may be significant errors associated with the techniques used for measurements, experimental evidence is provided for the existence of a compromised and anisotropic blood supply to many tumors. As a result, O_2-depleted areas develop in human malignancies which coincide with nutrient and energy deprivation and with a hostile metabolic microenvironment (*e.g.*, existence of severe tissue acidosis).

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http://www.washington.edu/news/2011/04/04/high-dose-of-oxygen-enhances-natural-cancer-treatment/

April 4, 2011 ***High dose of oxygen enhances natural cancer treatment***

Hannah Hickey
News and Information

"…An environment of pure oxygen at three-and-a-half times normal air pressure adds significantly to the effectiveness of a natural compound already shown to kill cancerous cells, researchers at the University of Washington and Washington State University recently reported in the journal Anticancer Research.

Annual wormwood, Artemisia annua L., yields the important antimalarial drug artemisinin. Researchers at UW and WSU are exploring its ability to treat cancer.***Scott Bauer, USDA Agricultural Research Service, Bugwood.org***

In the new study, using artemisinin or high-pressure oxygen alone on a culture of human leukemia cells reduced the cancer cells growth by 15 percent. Using them in combination reduced the cells growth by 38 percent, a 50 percent increase in artemisinins effectiveness.

“If you combine high-pressure oxygen with artemisinin you can get a much better curing effect,” said author Henry Lai, a UW research professor of bioengineering. “We only measured up to 48 hours. Over longer time periods we expect the synergistic effects to be even more dramatic.””

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http://www.sciencedirect.com/science/article/pii/0959804995005315

Role of oxygen free radicals in cancer development

D. Dreher, A.F. Junod **Abstract**

In aerobic life, oxidative stress arises from both endogenous and exogenous sources. Despite antioxidant defence mechanisms, cell damage from oxygen free radicals (OFR) is ubiquitous. OFR-related lesions that do not cause cell death can stimulate the development of cancer.

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This review discusses the effects of oxidative stress at the different stages of carcinogenesis. Mutagenesis through oxidative DNA damage is widely hypothesised to be a frequent event in the normal human cell. A large body of evidence suggests important roles of OFR in the expansion of tumour clones and the acquisition of malignant properties. In view of these facts, OFR may be considered as an important class of carcinogens.

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http://www.cancerfightingstrategies.com/oxygen-and-cancer.html#sthash.RXTNeJ5j.dpbs

Oxygen and Cancer: Low Oxygen Levels Breed Cancer... The link between **oxygen and cancer** is clear. In fact, an underlying cause of cancer is **low cellular oxygenation levels**.

In newly formed cells, low levels of oxygen damage respiration enzymes so that the cells cannot produce energy using oxygen. These cells can then turn cancerous.

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http://cancerres.aacrjournals.org/content/59/23/5863.long

The Hypoxic Cell

A Target for Selective Cancer Therapy—Eighteenth Bruce F. Cain Memorial Award Lecture 1

1. **J. Martin Brown**2

+ Author Affiliations: *Cancer Biology Research Laboratory, Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California 94305*

Abstract

It has been appreciated for more than 50 years that very low levels of oxygenation, or hypoxia, both protect cells from killing by X-irradiation and are present in solid tumors but not in normal tissues. Until recently, however, there has been no definitive proof that hypoxia in human tumors contributes to radiotherapy treatment failure. We now know that hypoxia in solid tumors is not only a major problem for radiation therapy but also leads to resistance to most anticancer drugs and, importantly, appears to accelerate malignant progression and increase metastasis. To date, efforts to overcome the problem of hypoxia have had only limited success. However, the recent development of new drugs that are nontoxic until they are activated in the hypoxic cell opens a new era. The first of these new drugs to be tested clinically, tirapazamine, a drug that is highly toxic to hypoxic but not aerobic cells, has already demonstrated efficacy in selective potentiation of cisplatin in

randomized Phase III trials with non-small cell lung cancer. The unique presence of hypoxic cells in human tumors provides an important target for selective cancer therapy.

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Introduction

Research on methods of overcoming the problem for radiotherapy of hypoxic cells in solid tumors has been ongoing for almost 50 years. During that time, interest among basic researchers has waxed and waned as promising new directions emerged, only to fail in clinical trials. However, as increasingly sophisticated concepts have replaced earlier, simpler ideas, the prospect of overcoming and eventually exploiting this fundamental difference between normal and malignant tissues appears more realistic. Recent clinical studies have for the first time unequivocally demonstrated that hypoxia in solid tumors is a major problem for radiotherapy, and that low oxygenation can accelerate malignant progression and metastasis, thereby creating a poorer prognosis irrespective of which cancer treatment is used. Development of new drugs that are selectively toxic to hypoxic cells, of which TPZ 3 is a prototype, has a solid theoretical and preclinical base and is also showing positive clinical results. This review will trace some of the important concepts and developments that have brought us to the present in this field.

Previous SectionNext Section

The Problem for Radiotherapy of Hypoxia in Solid Tumors

Although it had been appreciated for several years that lowering the oxygenation of tissues made them more resistant to damage by ionizing radiation (1) , it was the pioneering studies of Gray and colleagues soon after World War II that established the universality of the radiation resistance conferred by hypoxia as well as providing early insight into the mechanism of action. In their landmark paper, Gray *et al.* (2) showed that hypoxia conferred resistance to radiation damage of a wide range of cells and tissues using various end points. They showed further that it was the presence of oxygen at the time of irradiation that caused radiation sensitivity rather than any metabolic effects, as had been previously supposed. The oxygen effect may be unique in biology in having such a broad applicability: it applies to enzymes in solution; to bacteria; to yeast; and to plant and mammalian cells irrespective of their genetic background. A typical radiation killing curve for mammalian cells under aerobic and hypoxic conditions is shown in Fig. 1 ⇓ . The difference in radiation sensitivity between the aerobic and hypoxic cells, which is known as the oxygen enhancement ratio and is defined as the ratio of doses to produce the same level of cell kill under hypoxic to aerobic conditions, is normally in the range 2.5–3 for mammalian cells. Although this ratio may not seem large, the difference in cell kill for a given radiation dose can be several orders of magnitude, as can be seen in Fig. 1 ⇓ for a dose of 14 Gy (*dashed vertical line*). The reason for the universality of this effect is that oxygen reacts chemically with the fundamental biological lesion produced by ionizing radiation, a radical in DNA. Oxygen, being the most electron-affinic molecule in the cell, reacts extremely rapidly with the free electron of the free radical, thereby “fixing” (making permanent) the damage. In the absence of oxygen, much of the radical damage can be restored to its undamaged form by hydrogen donation from nonprotein sulfhydryls in the cells. This mechanism is shown in Fig. 1 ⇓ . Thus, ionizing radiation is severely compromised in its ability to kill hypoxic cells. This is true for all cell types, both normal and malignant. However, the degree of resistance can be changed somewhat by the nature of the radiation. Very densely ionizing radiation such as α particles shows no effect of cellular oxygenation on their killing ability, with particles of intermediate ionization densities such as fast neutrons having an intermediate effect (3) . This has been the motivation for developing neutron beams for therapy, but the expense and other problems of such modalities have prevented their widespread acceptance. For the foreseeable future, the vast majority of radiotherapy will be conducted with X-rays.

http://www.nature.com/nature/journal/v458/n7239/abs/nature07733.html#close

Nature **458**, 780-783 (9 April 2009) | doi:10.1038/nature07733; Received 6 September 2007; Accepted 18 December 2008; Published online 4 February 2009; Corrected 9 April 2009

Association of reactive oxygen species levels and radioresistance in cancer stem cells

Maximilian Diehn[1,2,12], Robert W. Cho[2,3,12], Neethan A. Lobo[2], Tomer Kalisky[8], Mary Jo Dorie[1], Angela N. Kulp[2], Dalong Qian[2], Jessica S. Lam[2], Laurie E. Ailles[2], Manzhi Wong[2], Benzion Joshua[4], Michael J. Kaplan[4], Irene Wapnir[5], Frederick M. Dirbas[5], George Somlo[9], Carlos Garberoglio[10], Benjamin Paz[10], Jeannie Shen[10], Sean K. Lau[11], Stephen R. Quake[8], J. Martin Brown[1], Irving L. Weissman[2,6] & Michael F. Clarke[2,7]

The metabolism of oxygen, although central to life, produces reactive oxygen species (ROS) that have been implicated in processes as diverse as cancer, cardiovascular disease and ageing. It has recently been shown that central nervous system stem cells[1, 2] and haematopoietic stem cells and early progenitors[3, 4, 5, 6] contain lower levels of ROS than their more mature progeny, and that these differences are critical for maintaining stem cell function. We proposed that epithelial tissue stem cells and their cancer stem cell (CSC) counterparts may also share this property. **Here we show that normal mammary epithelial stem cells contain lower concentrations of ROS than their more mature progeny cells. Notably, subsets of CSCs in some human and murine breast tumours contain lower ROS levels than corresponding non-tumorigenic cells (NTCs).** Consistent with ROS being critical mediators of ionizing-radiation-induced cell killing[7, 8], CSCs in these tumours develop less DNA damage and are preferentially spared after irradiation compared to NTCs. Lower ROS levels in CSCs are associated with increased expression of free radical scavenging systems. Pharmacological depletion of ROS scavengers in CSCs markedly decreases their clonogenicity and results in radiosensitization. These results indicate that, similar to normal tissue stem cells, subsets of CSCs in some tumours contain lower ROS levels and enhanced ROS defences compared to their non-tumorigenic progeny, which may contribute to tumour radioresistance.

[My questions: Can this be an issue of effective or not-effective **metabolism** of oxygen producing ROS as opposed to oxygen itself? Does metabolism of oxygen always produce ROS and only ROS? There is research on impaired cell metabolism contributing to cancer]

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Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach?
Nature Reviews Drug Discovery Review (01 Jul 2009)

http://www.nature.com/nrd/journal/v8/n7/full/nrd2803.html

Review *Nature Reviews Drug Discovery* **8**, 579-591 (July 2009) | doi:10.1038/nrd2803

Targeting cancer cells by ROS-mediated mechanisms: a radical therapeutic approach?

Dunyaporn Trachootham, Jerome Alexandre & Peng Huang

Abstract

Increased generation of reactive oxygen species (ROS) and an altered redox status have long been observed in cancer cells, and recent studies suggest that this biochemical property of cancer cells can be exploited for therapeutic benefits. Cancer cells in advanced stage tumours frequently exhibit multiple genetic alterations and high oxidative stress, suggesting that it might be possible to preferentially eliminate these cells by pharmacological ROS insults. However, the upregulation of antioxidant capacity in adaptation to intrinsic oxidative stress in cancer cells can confer drug resistance. Abrogation of such drug-resistant mechanisms by redox modulation could have significant therapeutic implications. We argue that modulating the unique redox regulatory mechanisms of cancer cells might be an effective strategy to eliminate these cells.

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T·H· Saey· More oxygen may lead to more tumors· Science News· Vol· 187, February 7, 2015, p· 6·

Breathing at sea level may be hazardous to your health, a new study hints. The research compared cancer rates for people at living at various elevations and found that lung cancer rates are lower at high elevations where the air is thinner.

If every person in the United States lived at elevations above 3,400 meters, such as atop Mount Hood in Oregon, there would be 65,496 fewer cases of lung cancer each year, researchers Kamen Simeonov and Daniel Himmelstein estimate. (In 2014, an estimated 224,210 new cases of lung cancer were expected to be diagnosed in the United States.) The findings could mean that lung cancer is linked to altitude — more specifically to the amount of oxygen in the air, the researchers report January 13 in *PeerJ*. Other cancers included in the study weren't linked to altitude.

[My question: If lung cancer is the only cancer that high altitude reduces, is it possibly due to strengthening the lungs? When it is harder to breathe, do lungs have to work harder?]