Anti-Warburg and Warburg Effects on Cancers

As biomedical research evolved, Otto Warburg’s theory for cellular respiration in relation to causes of cancer was widely accepted until the focus shifted to DNA and the genomic modeling of Watson and Crick.

Over the past decades, causes of chronic diseases have not been identified; i.e. until MCFIP developed an explicit and verifiable epigenetic model that incorporates homeostasis between minerals and elements. The model highlighted on the MCFIP website www.MCFIP.net provides the tools necessary for the global biomedical research community to identify causes of chronic diseases.

When MCFIP applied the principles of quantum mechanics to biomedical research, the following shortcoming of Warburg’s model as was as the DNA – RNA model of Watson and Crick became obvious:

**Warburg**

- The Warburg Effect included photosynthesis with chlorophyll – glucose conversion. Without chlorophyll and an alternative source for glucose in the cells of living creatures, cellular respiration could be reduced to the three gas interactions; i.e. carbon dioxide – oxygen – nitric oxide.
- Photosynthesis could be replaced by optogenetics. The process is complex but a high level overview is provided on the MCFIP website: http://www.mcfip.net/upload/Optomechanics%20(Explanation)%20x.pdf
- Other gases (e.g. carbon monoxide and hydrogen sulfide) interact with the ones identified by Otto Warburg.
Ongoing research has identified carbon monoxide (CO) and hydrogen sulfide as factors for cancers. Designations of anti-Warburg and reverse-Warburg have emerged. One of the most notable efforts to address those gases was the use of thalidomide; refer to the article affixed to this document. Reference to MCT1 in the article enabled us to link thalidomide to carbon monoxide; i.e. modeling of carbon monoxide and other bodily gases have identified MCT1 as a factor.

Details of these interactions are provided in the documents affixed to this article. However, due to complexity, interested parties are encouraged to discuss the process with MCFIP to avoid misunderstandings due to terminology.

**Watson – Crick**

In 2007, having applied quantum mechanics to biological sciences, it became obvious that a 5\(^{th}\) nucleobase existed, the complex algorithms were unnecessary and RNA theories were flawed. With that being said, without peer-reviewed research to support our hypothesis, it was necessary for us to set aside discussions that could lead to a new process that explains cellular level signaling that, if imbalanced, can lead to chronic diseases. However, having discovered the fact that minerals and elements are the foundation for cytokines\(^1\), MCFIP proceeded to develop models for testing of epigenetic interactions based on physical chemistry and to file patent applications for test configurations.

It was not until 2012 that researchers at Weill Cornell in NYC identified the existence of a 5\(^{th}\) nucleobase and claims were made that it was time to rewrite text books. While the shortcomings of DNA modeling that was based on crystallography have been validated scientifically, viable

\(^1\) [http://www.mcfip.net/upload/Small%20Molecule%20(Cell-Surface)%20Activities.pdf](http://www.mcfip.net/upload/Small%20Molecule%20(Cell-Surface)%20Activities.pdf)
and verifiable explanations for how RNA signaling of cellular mechanisms must be reconfigured have not emerged; except in the MCFIP website.

**Summary**

The Warburg Effect has been modified to exclude photosynthesis and it has been enhanced to encompass the five gases that regulate cell respiration and vascular signaling. The interactions between the gases are identified in US patent US 9,164,071: [http://www.uspto.gov/web/patents/patog/week42/OG/html/1419-3/US09164071-20151020.html](http://www.uspto.gov/web/patents/patog/week42/OG/html/1419-3/US09164071-20151020.html)

Applying physical science and homeostasis to biomedical research has enabled MCFIP to develop a website that provides verifiable examples of the primary causes of countless chronic diseases. Business executives are encouraged to challenge research and scientific support personnel to set aside dogma based on flawed theories. Without valid scientific principles that can disprove the modeling methods provided in the open source format on the MCFIP website, corporations are risking “disruption” and fiscal demise.

In other words, if solutions to mysteries surrounding causes of chronic diseases have not been identified through current genomic modeling and valid methods can be understood by applying bioinformatics using an explicit model, existing research methods must be reconfigured.

[https://www.sciencedaily.com/releases/2016/06/160617104926.htm](https://www.sciencedaily.com/releases/2016/06/160617104926.htm)

**Scientists discover mechanism of thalidomide**

Malformations, anti-cancer effects have a common mechanism

**Summary:**

June 17, 2016

Technical University of Munich (TUM)
In the 1950s, thalidomide (Contergan) was prescribed as a sedative drug to pregnant women, resulting in a great number of infants with serious malformations. Up to now, the reasons for these disastrous birth defects have remained unclear. Researchers at the Technical University of Munich (TUM) have at last identified the molecular mechanism of thalidomide. Their findings are highly relevant to current cancer therapies, as related substances are essential components of modern cancer treatment regimens.

Thalidomide was marketed as a sedative in West Germany and some other countries under the brand name "Contergan." 55 years ago, in 1961, it hit the headlines after having caused horrific deformations in unborn children. Between 5,000 and 10,000 children were affected worldwide. To this day, more than 2,000 victims across the world still live with the consequences of this tragedy. Soon after the discovery of these devastating side effects, the drug was withdrawn from the market. More recently, however, thalidomide is experiencing a kind of renaissance, as it was coincidentally discovered to inhibit the growth of certain tumors.

Since then, the two follow-up substances lenalidomide and pomalidomide have been approved for cancer treatment. Both thalidomide-derivatives are successfully used to treat certain bone-marrow cancers such as multiple myeloma. While showing stronger anti-tumor potential, they have fewer side effects than thalidomide. Despite this, they still pose a risk of causing severe birth defects and must not be taken during pregnancy.

Several proteins involved

Thalidomide, lenalidomide and pomalidomide are also known as immunomodulatory drugs (IMiDs). The name is derived from their ability to modify the body's immune response. Professor Florian Bassermann at the Department of Internal Medicine III of the TUM University Hospital and his team studied the molecular mechanism of IMiDs; their study has recently been published in "Nature Medicine." Bassermann is a Principle Investigator of the German Consortium for Translational Cancer Research (DKTK).

Other research teams had previously established that cereblon, a cellular protein, plays an important role in the function of IMiDs. However, the exact details as to how cereblon mediates the effects of IMiDs have only now been worked out by Prof. Bassermann and his team: Inside cells, cereblon usually binds to the proteins CD147 and MCT1. These two proteins typically occur in blood building and immune cells, and amongst other things, promote proliferation, metabolism and the formation of new blood vessels. In cancers such as multiple myeloma, tumor cells contain particularly high levels of CD147 and MCT1.
IMiDs "outcompete" proteins

As a so-called protein complex, CD147 and MCT1 always occur as a pair. However, to find their other half and become activated, they require the help of cereblon. Binding to the cereblon protein promotes development and stability of the complex, which in return stimulates cell growth and facilitates the excretion of metabolic products like lactate. In diseases such as multiple myeloma an increased abundance of this protein complex enables tumor cells to multiply and spread rapidly. If such a cancer is treated with IMiDs, the drug virtually displaces the complex from its binding to cereblon. As a result, CD147 and MCT1 can no longer be activated and vanish. "Ultimately, this causes the tumor cells to die," says Dr. Ruth Eichner, the study's first author.

Strikingly, the TUM scientists and a research team from the German Centre for Neurodegenerative Diseases (DNZE) were able to demonstrate that the disruption of the protein complex also causes the devastating birth defects. "The mechanisms are identical," Prof. Bassermann explains. "A specific inactivation of the protein complex resulted in the same developmental defects observed after thalidomide treatment." Without these two proteins, blood vessels cannot develop properly. This confirms the prevailing hypothesis that the typical Contergan-induced deformities are related to the reduced and abnormal formation of new blood vessels.

New treatment approaches

Direct clinical consequences can be drawn from the full correlation of clinical efficacy of IMiD treatment with the observed molecular effects. "The disappearance of the protein complex could only be observed in patients that had responded well to this type of treatment," says Florian Bassermann. This could be helpful in assessing a patient's response before starting the actual treatment: A sample of the patient's tumor cells could be taken into culture and treated with IMiDs. If these cells then showed a disruption of the complex, the patient will most likely benefit from IMiD treatment.

The results of this recent study also warrant new cancer therapies without IMiDs. The protein complex is a particularly attractive target for tumor treatment, as it is mainly found on the surface of cells and virtually links the inside to the outside of the cell. Therefore, the inactivation of the complex can easily be achieved using specifically produced antibodies and other distinctive drugs -- a possibility that is currently being explored by Prof. Bassermann and his team.

Story Source:
The above post is reprinted from materials provided by Technical University of Munich (TUM). Note: Materials may be edited for content and length.

Journal Reference:

**MCFIP** – Biomedical researchers are unaware of interactions and imbalances of cellular levels substances. Bodily gases, see below, are an example.

Dependent upon imbalances, carbon monoxide could be beneficial or lethal.

Details of the interactions between these gases and outcomes (including vascular abnormalities) can be discussed with interested parties.
Carbon Monoxide May Help Shrink Tumors, Amplify Effectiveness of Chemotherapy

Dec. 4, 2013 — 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. "Important 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."
monoxide are included (refer to the second illustration), the ‘anti-Warburg’ effect occurs.

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. MCFIP – There are three members of this family; i.e. HO1-1 through HO-3 (HMOX 1 – 3)

"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." MCFIP – Research regarding CO and tumors must take the following into account:

- Was the lack of CO the cause of the tumor formation? And, if so, was it attributable to disruption of the signaling molecules, the disruption of the cells in the carotid body or in the posterior lobe of the pituitary gland, the inability for ferroelectric activity to convert carbon dioxide to carbon monoxide or another TBD reason?
- Caution must be exercised with regard to the use of CO; i.e. levels must be tested in relation to the other bodily gases to ensure targeted drug therapy.

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. MCFIP – The specific interactions between the gasotransmitters will have to be determined by members of the scientific community. It should be noted that in some instances, cancers can be attributable to
inadequate NO and CO will increase those levels. Accordingly, in those instances, the cause would be NO deficiency; possibly due to excessive H2S.

Studies indicate levels of NO are impacted differently by levels of CO; i.e. similar to the impact alcohol has on NO. Accordingly, this factor must also be addressed by thorough research.

"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."

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**Carbon Monoxide - Carbon Dioxide Interface**

When the article affixed to this document indicated monocarboxylate transporter 1 (MCT1) played a critical role in insulating axons, we attempted to model the constituents of this signaling molecule. Unfortunately, the lack of adequate studies prevented us from being able to formulate any definitive hypothesis or to identify the constituents of these signaling molecules. However, we were able to identify the following information for consideration by scientists who pursue the disciple of signaling molecule dynamics.
• There are 4 members of the MCT family and NBC appears to be a fifth member (sodium bicarbonate cotransporter).

• **These signaling molecules are associated with carbon monoxide - carbon dioxide conversions**

To date, despite considerable efforts to identify the roles of the gasotransmitter carbon monoxide with regard to signaling molecule synthesis when subjected to catabolic activity, these findings are the first clues that we have found. Accordingly, we have merely recorded these findings for consideration as part of research by members of the scientific community.