3 Bromopyruvate And the Metabolic Approach to Cancer

In February, I traveled to Baltimore to interview Peter Pedersen, PhD, and Young Hee Ko, PhD, concerning the metabolic approach to cancer and their formulation of a novel anticancer compound, **3-bromopyruvate (3BP).**

Pedersen is a legendary figure in the field of cancer metabolism. More than any other living scientist, he has elucidated the various ways--normal and abnormal--that a cancer cell generates its energy. Energy production fuels all cells, including cancer cells. Thus understanding the energy production factories inside cells offers the greatest hope for controlling the growth and spread of cancers.

Pedersen is a seasoned professor of biological chemistry and oncology at the Johns Hopkins University School of Medicine in Baltimore. In addition, he is a member of the Sidney Kimmel Cancer Center, and the Center for Obesity and Metabolism Research, at the same institution. Ko is a former Hopkins researcher who now directs KO Discovery LLC at the University of Maryland's biomedical research park (BioPark), where we had our meeting.

Pedersen was born in Oklahoma to a part-Cherokee mother and a Danish-American father. He attended American Indian schools through high school and showed an early aptitude for biology. He had the advantage of having an older brother, Lee, who was already determined to be a scientist. After graduating from the University of Tulsa in Oklahoma, both went to graduate school at the University of Arkansas. Here, Lee majored in theoretical chemistry and Peter in biochemistry. Lee subsequently carried out postdoctoral work at Harvard and later became a celebrated professor at the University of North Carolina.

While still at the University of Arkansas, Peter Pedersen focused on work related to muscle contraction while learning in required laboratory experiments about the great German biochemist/physiologist Otto H. Warburg, MD, PhD. Warburg won the 1931 Nobel Prize for his pioneering work on cancer metabolism.

Warburg is generally considered the preeminent biochemist of the first half of the 20th century (Nelson 2008) and was well known for developing an instrument known as the "Warburg apparatus" that was used to measure at a given temperature the amount of gas; for example, oxygen, produced or absorbed by various tissues and cancerous tumors.

Warburg's most important discovery was that most animal cells produce energy (conserved in the form of adenosine triphosphate, or ATP) by first converting glucose into carbon dioxide and water. This is done through a process called oxidative phosphorylation, or OxPhos for short. OxPhos, which takes place in specialized cellular bodies called mitochondria, is the culminating step in cellular respiration. But cancer,

Warburg found, also utilizes an abbreviated form of energy generation called glycolysis (also known as fermentation). This process produces energy (ATP) by converting glucose into lactic acid. As Pedersen summed it up in our interview: "Most normal animal cells rely heavily on the mitochondria for their energy needs but when transformed to become cancer cells, particularly the most malignant, they rely significantly on both mitochondria and glycolysis."

This ability to use both forms of energy generation gives a cancer cell flexibility. It can survive where oxygen is abundant but also where it is in short supply (such as in the interior of a dense tumor). Plus, glycolysis benefits tumors in other ways. For instance, the production of lactic acid as a byproduct helps tumor cells penetrate neighboring tissues or even spread (metastasize). Scientists at the University of Arizona have found that culturing cancer cell lines in even a slightly acidic medium "caused dramatic increases in both migration and invasion" (Martinez-Zaguilan 1996). The cells became more cancerous.

Pedersen Arrives at Hopkins

Peter Pedersen began his career as a postdoctoral fellow in the Department of Biological Chemistry of Johns Hopkins Medical School (ranked the nation's top medical school for research). He had the good fortune to work under Albert L. Lehninger, PhD, a legendary figure in biochemistry and author of Principles of Biochemistry (now in its 9th edition). After completing postdoctoral work in Lehninger's laboratory, Pedersen focused on understanding how mitochondria make ATP, the major energy source for all cellular--energy requiring processes. As a new faculty member, he then set out two long-term goals related to the study of cancer:

1. to explain at a cellular and molecular level the "Warburg effect"; i.e., increased metabolism of glucose to lactic acid even in the presence of oxygen. (That is, even though the mitochondria of cancer cells are capable of making sufficient ATP to fuel/power their growth via OxPhos, such cells also make significant use of glycolysis to help make this ATP.)

2. to discover a drug that inhibits both of cancer's energy-producing factories, OxPhos and glycolysis, while leaving normal cells alone. Then, without their source of energy, the cancer cells that comprise tumors will die quickly and the tumors will disappear.

Needless to say, while goal #1 would be a major advance for science, goal #2 would be an even greater advance for humanity. We are, after all, talking about finding an effective and minimally toxic treatment for almost all cancers! For the next almost four decades, Pedersen and his coworkers struggled with this, among other problems.

A String of Discoveries

Along the way, Pedersen and his coworkers made at least a dozen major discoveries in the field of cancer metabolism. Without going into great detail (all of which is available in

the standard medical literature), I will sketch the outlines of several below.

1970: Pedersen and his group discovered that cancers exhibiting the Warburg effect have a reduced respiration rate relative to their tissue of origin. However, this reduced respiration rate is not due to defective mitochondria but to a markedly reduced number of mitochondria (Schreiber et al. 1970).

1977: The Warburg effect mainly results from a less commonly used variant (called an isoform) of the enzyme hexokinase, which is markedly elevated in cancer and binds to the outer membrane of the mitochondria (Bustamante and Pedersen 1977).

1984: In cancer cells that exhibit the Warburg effect, there is a division of labor in producing the required energy. This central task is shared by two energy-producing factories: OxPhos and glycolysis. In some liver cancer cells, for example, about 60% of the energy comes from glycolysis and 40% from OxPhos in the mitochondria (Nakashima et al. 1984). This is a major point, as many people believe that cancer cells are fueled exclusively by glycolysis. However, malignant cells actually use both methods. Thus any agent that is postulated to cut the energy supply of a tumor must eradicate both energy-producing factories while leaving normal cells unharmed.

1988: The form of hexokinase (an enzyme) that is involved in the Warburg effect is hexokinase 2 (Hk-2; Nakashima et at. 1988). Other scientists later discovered that Hk-2 is bound to the outer mitochondrial membrane, where it renders cancer cells immortal.

2001: Now we come to the most important of all the discoveries in Pedersen's lab. This was the finding, made by his colleague Ko, that in cancer cells a small molecule called 3-bromopyruvate (3BP) inhibits both glycolysis and OxPhos (Ko et at. 2001). This fulfills the second task that Pedersen set himself to accomplish in the 1960s.

Ko was born in South Korea. She completed her master's degree in nutritional physiology at Iowa State University and graduate school in biochemistry/biophysics at Washington State University. In the 1990s she came to Johns Hopkins as a postdoctoral fellow. She and Pedersen have been working together since 1991 (Thomas 1992).

Asked by Pedersen to find a drug that would target both types of energy production, Ko thought of a substance that she had worked with as a graduate student. This was 3BP. In our conversation, Young referred to 3BP as a kind of "Trojan horse," which tricks the cancer cell into thinking that it is receiving a useful nutrient, when in fact it is receiving a powerful cancer-killing molecule.

Given 3BP, as specially formulated by Ko, tumor cells are quickly destroyed, while normal cells are left unaffected. This is because, unlike tumor cells, normal cells do not have elevated levels of monocarboxylic acid transporters (MCTs). As Ko and Pedersen explained it, MCTs are the transporters that allow 3BP to get inside tumor cells. Once inside, 3BP quickly destroys both of the tumor cells' power plants (glycolysis and OxPhos). The tumor cells die quickly via either apoptosis or necrosis (two common

methods of cell death), attended by a rapid depletion of their energy.

2004: Ko and Pedersen, with half a dozen coauthors, published the first account showing that 3BP is able to completely destroy tumors in all animals tested, without causing noticeable toxicity. The tested animals lived out their normal lifespans without the cancerous tumors reappearing (Ko et al. 2004). Pedersen says that, to his knowledge, this was the first time in history that a small molecule was shown to have such remarkable cancer-curative effects.

2002: At around the same time, Ko and colleagues also participated in a study that showed that the intra-arterial delivery of 3BP formulated by Ko prevented cancer metastases (spreading) from the liver to the lungs (Geschwind, Ko, et al. 2002) and likely to other tissues as well. These are remarkable findings, unprecedented in cancer research. Prominent scientists have spent lifetimes in trying to discover agents with only a small fraction of the potential in this molecule. The significance of this finding cannot be overstated, since it is well known that most deaths from cancer result from its metastasizing to other organs, and not from the primary growth.

2012: Ko showed that 3BP can work in humans. In a recent paper, 3BP was tested successfully in a few people, with no obvious signs of toxicity. One young teenage patient from Europe, who had been sent home to die by his doctors, lived for another year after taking 3BP. He even was able to take a vacation to the US with his parents, where he participated in a clinical lecture at Johns Hopkins. His death was not due to the primary cancer, Ko told me, but to an infection (Ko et al. 2012).

The authors also showed that 3BP was capable of stimulating liver regeneration after first killing the primary liver tumor. This is believed to be the first time that a chemical agent was able to have such an organ-regenerating effect (Ko et al. 2012)

2013: In January, the Nobel laureate James D. Watson, PhD, codiscoverer of DNA's "double helix" and the most renowned scientist in the world today, paid homage to 3BP and, by extension, to the work of Pedersen and Ko. He wrote:

> **3-bromopyruvate**, the powerful dual inhibitor of hexokinase as well as oxidative phosphorylation, kills highly dangerous hepatocellular carcinoma [liver cancer], cells more than 10 times faster than the more resilient normal liver cells and so has the capacity to truly cure, at least in rats, an otherwise highly incurable cancer.

In his paper Watson referenced the 2004 Ko et al. manuscript.

Pedersen's career in biological chemistry essentially began in 1961 when he gave a seminar on the discoveries of James Watson and Francis Crick about the double-helical structure of DNA as one of his last requirements as an undergraduate chemistry major at the University of Tulsa. How ironic, then, that 50 years later Prof. Watson returned the

compliment, and publicly paid homage to Pedersen and Ko's work with 3BP. As Pedersen put it, "Perhaps it is fair to say that he or she who follows in the footsteps of other great scientists may one day have them following in their own footsteps."

2013: Prof. David M. Sabatini, a member of the Whitehead Institute of Biomedical Research (Cambridge, MA), and his colleagues recently confirmed Pedersen and Ko's work with 3BP. Interestingly, but importantly, they made their confirmation without corresponding with either Pedersen or Ko before publishing their confirmatory paper (Birsoy 2013). Sabatini and colleagues wrote:

> Our results identify a potential biomarker for 3-BrPA [another abbreviation for 3BP] sensitivity and provide proof of concept that the selectivity of cancer-expressed transporters can be exploited for delivering toxic molecules to tumors. (ibid.)

Scientists would understand that the "toxic molecule" in question, 3BP, is only "toxic" in relation to cancer cells. Normal cells are spared as they have fewer transporters capable of moving 3BP into the cells.

Conclusions

Readers will of course be happy to hear that such a promising new agent as 3BP has emerged from Johns Hopkins School of Medicine and has been confirmed by scientists at other institutions, such as the Whitehead Institute. 3BP is not only important in its own right but serves as "proof of principle" for the idea that one can manipulate metabolism to interfere with the growth of cancer. Pedersen believes in metabolic therapy and wrote the introduction to Thomas Seyfried's provocative recent book, Cancer As A Metabolic Disease.

On the other hand, there is a dark side to this story. First, after nearly a decade, 3BP remains unavailable to cancer patients. It is not even in formal clinical trials in the US. Perhaps even more outrageous still is that NIH study sections assigned to review two of Pedersen's cancer-related renewal applications in recent years have rejected them several times. The few (2 or 3) peer reviewers assigned to look at each of their assigned applications have the power early on in meetings at the NIH (or some location nearby) to recommend its rejection. Once this is recommended, the application is thrown in the trash without a formal review; that is, a discussion involving not only the two or three assigned reviewers but the entire study section (15 to 30 scientists). This is simply an outrage, not only to the public at large but to those study section members who never had the opportunity to really read and discuss fully the applications.

Perhaps an "angel" will appear to fund further necessary research into the remarkable

activity of this substance. Or perhaps the issue will need to be slugged out in newspapers and websites, or in the halls of Congress, as has happened before in the history of cancer. However it happens, 3BP deserves further study and fair, honest, and thorough clinical trials so we can finally learn more about its potential as a simple, nontoxic or surely less toxic treatment for cancer.

Finally, it should be noted that Dr. Pedersen sent a personal letter to President Obama about this matter on January 22, 2013. The president's mother died of ovarian cancer at the early age of 53. Months later, Dr. Pedersen had still received no response from the president. If the federal government is seriously interested in ending the scourge of cancer it should pay attention to the exciting things that are happening in Baltimore.
SOURCE: Cancer Decisions – July 2013

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