Non-steroidal Anti-Inflammatory Drugs (NSAIDs) and Cancer Treatment

Common anti-inflammatory drugs ibuprofen, aspirin and acetaminophen have recently been intriguing scientists with their anticancer properties. Ibuprofen is found in many over the counter pain medications such as Advil and Motrin. These medications are taken daily across the world to treat headaches, reduce swelling, and other every day aches and pains. Additionally, aspirin is also helpful in the prevention of some cardiovascular diseases (Pereg, 2005). Aspirin and ibuprofen were administered to groups of patients with various incident cancers against similar groups given placebos. A placebo is a pill that has no medical effect and is intended to keep the patients in the dark as to who is receiving the treatment. These studies showed a slightly decreased risk of developing those cancers. (Meier, 2002).

Scientists discovered that a chiral variation of Ibuprofen, also known as iso-butyl-propanoic-phenolic acid, inhibits the activity of a protein called alpha-methylacyl-CoA racemase (abbreviated AMACR) (Brown, 2011). The term chiral refers to a molecule that is not superimposable on its mirror image. AMACR is overproduced in tumors of the liver and prostate while in normal tissues it is produced in very low quantities. This anomaly is caused by a mutation in a particular oncogene, or cancer causing gene, called CTNNB1. (Sekine). AMACR converts ibuprofen’s R-enantiomer to its S-enantiomer which results in AMACR being unable to promote the growth of a tumor. (Brown, 2011).
AMACR plays an important role within a cell’s metabolism. It regulates the metabolism by catalyzing the chiral inversion of 2-methyl-fatty acyl-CoA esters found in lipids, or fats, in a human’s diet (Lloyd, 2008). The 2-methyl-fatty acyl-CoA esters are a derivative of the food a cell takes in but cannot digest (Zha, 2003). AMACR breaks the food molecule down, usually lipids, into a compound that is more usable by the mitochondria and peroxisomes. (Lloyd, 2008). Mitochondria are the “power plants” of the cell that convert food into energy. However, some food molecules are not readily used by the mitochondria so they are sent to the peroxisomes to be broken down before they are used by the mitochondrion. According to the Merriam-Webster dictionary, a lipid is any of various substances that are nonpolar, will not readily dissolve in water, with proteins and carbohydrates constitute the principal structural components of living cells, and that include fats, and waxes. From there, the mitochondrion creates usable energy for the cell. The conclusion may be made that if the level of AMACR available is high, there will be a high amount of energy produced by the mitochondria.

In order for a cell to divide, it needs energy. Cancer cells divide at abnormally high rates so they require considerably more energy than a normal, healthy cell. The presence of high levels of AMACR is not surprising since it is one of the key enzymes needed to break down lipids for the cell to convert into energy (Lloyd, 2008). The known presence of high AMACR levels in cancerous cells can be used help doctors recognize cancers early. Scientists have begun to recognize AMACR as a diagnostic marker for prostate cancer and will soon be using it for other cancers as well (Zha, 2003). The purpose of a diagnostic marker is to help doctors diagnose a particular illness. Doctors can now test levels of AMACR to determine if a patient may or may not have prostate cancer.

Ibuprofen is activated by the change from its R-enantiomer to its S-enantiomer. An enantiomer is one of two stereoisomers that are mirror images of each other but you cannot superimpose them upon each other. The enzyme responsible for activating Ibuprofen is known as ibuprofenoyl-CoA
epimerase. It turns out that ibuprofenoyl-CoA epimerase is the same as AMACR, so a team of scientists from the University of Bath in the UK decided to test how AMACR reacts to Ibuprofen. (Lloyd, 2008. Brown, 2011). Scientists simply converted a sample of Ibuprofen into its Coenzyme A (CoA) esters so that AMACR had something to bind to. Then they observed the result. They found that AMACR was bound very tightly by the R-enantiomer of its CoA ester converting it into its S-enantiomer. Interestingly, while AMACR is busy performing the chiral inversion of Ibuprofen, it cannot promote the growth of a tumor. (Brown, 2011).

Aspirin, or acyl-salicylic acid, has been shown to slow the progress of tumors in the several different types of cancers, including but not limited to pancreatic, lung, cervical and colorectal cancers. Aspirin inhibits the function of an enzyme called cyclooxygenase (COX). COX has two forms, COX-1 and COX-2. COX-1 is responsible for everyday maintenance functions of the cells while COX-2 is activated in response to inflammation and is used structurally in some cells such as the intestinal cells. Increased levels of COX-2 are found in cancerous cells and doctors believe it to be another diagnostic marker like AMACR mentioned above. (Pereg). COX-2 has been shown to increase the probability of metastasis and decrease apoptosis, or programmed cell death. It was also found that the absence of the gene coding for COX-2 reduces the number of cancerous polyps in mice, according to Wright (2001).

By inhibiting the functions of COX-1 and COX-2, Aspirin stops arachidonic acid from being converted to prostaglandin and thromboxane (Pereg, 2005). Arachidonic acid is important for used in
muscle and brain cells. Prostaglandins are found in nearly all nucleated cells and are important for cell signaling purposes. Thromboxane is involved with the narrowing of the blood vessels and the clotting of platelets. Thromboxane and prostaglandins directly affect the cells on the inside of the blood vessels of a human thus promoting the metastasis of cancer cells (Pereg, 2005). Metastasis occurs when part of a tumor breaks off and travels via the circulatory or lymphatic vessels to other parts of the body. From there, the cancerous cell will slip through a wall of a vessel and begin to divide again, creating another tumor.

The enzyme COX-2 has been shown to reduce the cells ability to perform apoptosis, a cell suicide of sorts. Apoptosis is a mechanism put in place to prevent the spread of abnormal or unhealthy cells. Cancer cells with a high level of COX-2 show a high resistance to apoptosis thus permitting the tumor to grow. The bottom line is that COX-2 is associated with advanced cancer. (Pereg, 2005).

Scientists figured out that if they could find a way to inhibit COX-2, they may be able to slow tumor growth. Aspirin has been shown to not only inhibit the pro-cancer functions of COX but to irreversibly change their structure. Aspirin changes the structure of COX-1 by adding an acetyl group, or COCH₃, to it. This inhibits the clotting function of COX-1 and is the reason for aspirin’s effectiveness against cardiovascular disease. Aspirin also acetylates COX-2 which has twice the anticancer defenses. This results in the inability of COX-2 to form prostaglandins and the production of a tumor suppressing compound. (Gardiner, 2003).

Acetaminophen is another common NSAID that has been studied to analyze any possible anticancer effects it may have. However, the results for this molecule are considerably less exciting. It has been shown that acetaminophen contributes a very slight decrease in risk for breast cancer and ovarian cancer in women, but other studies have been

![Acetaminophen Molecule](image)
inconclusive. However, there is actually a very slight negative association between long term acetaminophen use and colorectal cancer. (Meier, 2002). Acetaminophen has less anti-inflammatory agents than most other NSAIDs. This is because acetaminophen inhibits a COX-3 enzyme which is a variation of the COX-1 mentioned in previous paragraphs but it does not affect the COX-2 enzyme. This could perhaps be the reason that acetaminophen does not affect different cancers as much as ibuprofen or aspirin. (Harris, 2003). More studies must be performed in order to draw a reasonable conclusion about the anticancer properties of acetaminophen.

There are many negative side effects to prolonged usage to NSAIDs including damage to the liver and gastrointestinal ulcers. (Brown, 2011. Wright, 2001). Ibuprofen has been shown to really do a number on the liver and aspirin inhibits one of the structural enzymes in the lining of the digestive tract. (Gardiner, 2003). The theories about NSAIDs anticancer properties are still in the early stages and require several more years of testing before they can be advertised as anticancer drugs. Many scientists are not sold on the validity of the theory. There is still a great deal of skepticism on the true effectiveness of the treatment as some studies have been inconclusive. The hazardous side effects of these medications are something to be considered. In essence, one should not be taking ibuprofen for an extended period of time thinking that they are fighting cancer.

Cancer is not just a single disease that affects different areas of the body as one might think. It is an umbrella term for a plethora of different diseases that all have one thing in common: uncontrolled cell growth. Scientists are trying to find ways to inhibit that cell growth. Regardless of the side effects, these discoveries have open new ways of thinking in the area of cancer treatment. Perhaps a cure is simpler that scientist have anticipated. Prostate cancer has one of the highest death rates among males and the risk of prostate cancer can be dramatically reduced by a simple over the counter medication (Lloyd, 2008). The same is true with aspirin and colorectal cancers. The inconclusive results of
acetaminophen are important as well because we now know what doesn’t work to inhibit cancerous cells. This helps to narrow the number possible cures ever so slightly to progress towards a highly functional treatment. Because cancer covers such a wide range of diseases, a wide range of treatments must be found. Cancer continues to be one of the top killers in the world, and a safe cure remains ever elusive to scientists. The search goes on.
References


