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Fighting Cancer: Inducing Apoptosis in Cancer Cells

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Cancer is one of the leading causes of death in the world today. Almost everyone has been affected by cancer in one way or another. At the forefront of cancer research today is finding safe and effective ways to induce apoptosis in cancer cells. Recently, researchers have uncovered three mechanisms in which this can be accomplished. One is by using Artepillin C to activate TRAIL in cancer cells. Another focuses on increasing the effectiveness of radiotherapy by reducing the effects of IAPs. The third proposed treatment uses decitabine to cause ROS to start the apoptosis process. All three experiments show great promise. Even though each has its flaws, with continued research surrounding the mechanisms and symptoms of the treatments, there is hope that one day a cure for cancer will be found..

Introduction

"You have cancer." With just these three simple words from a doctor, a life can be turned upside down. Millions of people worldwide are diagnosed with cancer every year, and one would be hard pressed to find an individual (especially in the United States of America) who has not been impacted by cancer either directly or indirectly. Ever since cancer was first discovered, billions of dollars has been spent on research to try and develop a drug or treatment that will "cure" all cancer patients. Although one has not been found, researchers are making great strides in both understanding the mechanisms of a cancer cell and developing safer and less invasive treatment options against this horrendous disease.

As our understanding of cancer has improved, ways to fight cancer have also improved. Today, research is focused on ways to induce cancer cells to undergo apoptosis (programmed cell death) (1). A tell-tale sign of a tumor (a grouping of cancer cells) is when it does not undergo apoptosis on its own. By forcing a cancer cell to kill itself, the tumor can be decreased in size or even eliminated.(1) In recent months, three new treatments have been developed that seek to induce apoptosis in certain types of cancer cells. One involves activation of a cells tumor-related apoptosis-inducing ligand (TRAIL) in prostate cancer cells (3). Another involves ways to get around Inhibitor of Apoptosis proteins (IAP) and their negative effects on the effectiveness of radiotherapy (1). The final treatment fights leukemia by inducing apoptosis by using radioactive oxygen species (2). While none of these three treatments are anywhere close to the cure-all treatment that humanity has been searching for, they are progress, and when it comes to cancer research, any progress is good progress.

Recent Progress

Many developments in inducing apoptosis have come in the past year, especially as it pertains to the three possible treatment options mentioned above. In one experiment, researchers showed the drug artepillin C (a compound found in Brazilian green propolis) can be used to activate TRAIL mechanisms in prostate cancer cells and therefore can induce apoptosis in the cancer cells (3). It has been known by natives that the green propolis has had anti-cancer properties. To uncover the compound responsible for this property, researchers isolated each compound in the Brazilian green propolis and tested it on prostate cancer cells *in vitro* (3). They used prostate cancer cells

because they have been found to commonly be TRAIL-resistant. Upon doing this, they saw that artepillin C was the only compound that reduced the number of cancer cells, and thus concluded it must be the compound responsible for the anti-cancer properties of the green propolis. The researchers also discovered during the experiments that artepillin C works by the upregualtion of the TRAIL-R2 receptor, which is one of the mechanisms that tells the cell that it is time to die. Once the TRAIL-R2 receptor is initiated, several caspases (which are highly involved in the mechanism of apoptosis) also start to function. This experiment showed how effective artepillin C can be in fighting tumors and also the mechanisms by which it functions (3).

Radiotherapy is one of the most common forms of treatment of cancer today. Its goal is to induce apoptosis in cells. One of the huge problems with radiotherapy is that many cancer cells are radioresistant, and thus radiotherapy is ineffective (1). Researchers have recently found the radioresistance is due to in large part to IAP's, which inhibit the cell from undergoing apoptosis even though their DNA has been damaged by the radiation. It is thought that IAPs accomplish this by inhibiting several of the caspases in the cycle of apoptosis, but the exact mechanisms are largely unknown (1). Experiments have shown that XIAP (one of the most common IAP) can be inhibited by embelin, and using embelin along with radiotherapy greatly enhances the effectiveness of the radiotherapy. Another technique for overcoming IAPs is to flood the sail with SMAC, a molecule that increases caspase sensitivity in the cells and leads to a greater likelihood of apoptosis occurring (1). Although these two treatments show promise, a true combatant against IAPs will not be developed until the mechanisms of IAPs and exactly how they work in a cell are more fully understood.

The last recent discovery involving apoptosis in cancer cells are related ROS. The oxygen radicals (OH^-, $^1O_2$, O_2^-, and H_2O_2) have been found to induce apoptosis in cells by activating several caspases that start the process of apoptosis (2). Researchers have shown that using Decitabine (a DNA inhibitor) on cancer cells can cause apoptosis and that this is done by ROS activating caspases. Decitabine works by causing the cytoplasm to shrink, the chromatin to condense prematurely, and the DNA to degrade (2). In the experiment, Decitabine was exposed to human leukemia cells at various concentrations and time intervals. It was shown that the longer the cells were exposed to decitabine the more effective the drug was. It was also shown that the higher the concentration of the drug the better it worked. Lastly, the experiment showed that the cause of decitabine-induced apoptosis is ROS molecules (2). This is accomplished by the activation of caspases. ROS seem to be a very promising avenue for future cancer research in hopes of finding a cure for cancer.

Discussion

One cannot stress the importance of cancer research in today's world. Cancer is everywhere. One can hardly turn on the news without hearing about an amazing individual's life brought to a premature end by cancer. The three treatments for cancer above all have one thing in common and that is they all in some way or another induce apoptosis by the activation of caspases. One can conclude that the caspases must be important in apoptosis. Unfortunately, the mechanisms surrounding caspases are not understood well at all (3). It would seem that future research should focus on understanding how caspases work. Once the mechanism are fully understood, a drug could be developed that would work a whole lot better than anything currently on the market today. Each of the treatments have some very positive things about them. Artepillin C is good because it only affects cancer cells, not "normal" cells. Inhibiting IAPs shows promise because it can be used alongside radiotherapy to greatly enhance radiotherapy's effectiveness. ROS is something that is found naturally in the body and are produced by cellular respiration, thus they are always present in a cell (2).

Even though these treatments are very promising, they all have several faults in them that will require many studies before a possible cure could be developed. It has already been mentioned that the pathways of caspases are poorly understood. This is something that needs to be addressed before any of these treatments goes into human testing. This brings up another major flaw in the experiments: lack of human testing. None of the experiments were performed on an actual human individual. They were all done *in vitro*. To be able to fully understood the effectiveness and the side effects of all these proposed treatments, one has to see how they react with the countless other chemical processes in the body and make sure that none of the vital processes are inhibited in any way. IAPs are practically problematic because they are one the least understood mechanisms in the human body (1). There are several different IAPs as well as several different IAP inhibitors in the body and it is unclear which of these are most important in inducing apoptosis. Future research should focus on understanding IAPs better. This will lead to better ways to circumvent them and reduce radioresistance in cancer cells. One final fault is that all of these experiments were focused only on one particular type of cancer. Further research should be done to find a way to use these treatments in a way that will work for all cancers, not just a select few. Even with these faults, the findings of these experiment show great progress in cancer treatment by means of apoptosis. If researchers

keep developing the treatments explained in this review, one can hope that one day cancer will be as curable as the common cold. If this happens, society as we know it will be a much better place.

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