Promising Advancements in Modern Cancer Treatment

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Biology 597

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May 3, 2014

Chemotherapy is just medieval. It's such a blunt instrument. We're going to look back on it like we do the dark ages.— Dr. Eric Topol (Unreferenced, see "Notes")

Cancer afflicts over a million Americans every year and proves fatal to nearly half of those afflicted[1]. Over the years, scientists have made great strides in understanding the disease, but cancer's widely varied and adaptive nature has made finding a cure nearly impossible. Fortunately, scientists have achieved greater success in controlling cancer, and several promising advancements may soon overtake the traditional treatment options of chemotherapy and radiation. Two of these advancements, anti-cancer drugs targeting out-of-control cell-growth signaling enzymes and multi-drug resistance (MDR) proteins, may soon relegate the traditional options of chemotherapy and radiation—along with their extremely detrimental side effects—to the past.

Since the 1940s, nonsurgical cancer treatment has consisted almost exclusively of chemotherapy and radiation. These treatments function by destroying rapidly proliferating cells throughout the body, and are detrimental to cancer because, by its very definition, cancer is a mass of rapidly dividing invasive cells. Unfortunately, there are a number of other cell types within the body that also divide rapidly, such as hair, skin, and epithelial cells, all of which suffer the same fate as cancer cells when these treatments are used. Additionally, chemotherapy causes a vast array of harmful side effects, including immunosuppression, fatigue and nausea, neurological disorders, and organ damage[2], which, even if the cancer is contained, may negatively affect the patient's quality of life.

Despite these harmful side effects, chemotherapeutic drugs would be a viable option if they were effective at completely removing cancer from the body. However, the 1997 discovery of cancer stem cells[3] proved that this is not the case. Cancer stem cells behave in much the same

way as other stem cells, with the ability to differentiate into various tumor cells as required. This allows cancer stem cells to adapt as necessary based on environmental conditions, and often overcome adverse effects caused by treatment. More detrimentally, cancer stem cells propagate slowly, so they are not targeted by chemotherapy or radiation. Thus, there is always the possibility of relapse for patients who have "successfully" undergone chemotherapy.

Fortunately, alternate options are becoming available that seem to be more effective than traditional treatments at removing cancer, while simultaneously eliminating many of the harsh side effects. At the forefront of these new treatment options are designer drugs targeting enzyme proteins whose overactivity have been shown to cause cancer. To understand anti-enzyme drug therapy, we must first understand the structure and function of these pro-cancer enzymes. Cancer develops primarily through genetic mutations that alter the body's cellular equilibrium and allow cells to proliferate and migrate without restriction. These requirements, dubbed the "hallmarks of cancer[4]," are required for the successful development of the disease. Specifically, for cancer to arise, it must: secure blood supply for growing cells via angiogenesis, allow for unlimited and unrestricted division by manipulating the cell cycle and telomeres, overcome growth restrictions, prevent cell suicide, and invade surrounding tissue or colonize new sites in the body. These changes require multiple genetic mutations and are regulated by a wide variety of enzymes, many of which are specifically altered in cancer. These specific alterations are the backbone of enzyme-directed cancer treatment research.

Enzyme therapy works by targeting and restricting the cancer-specific enzymes required to sustain cancer's development and longevity. By disabling the mutated enzymes that make the hallmarks of cancer possible, the disease is prevented from further development, as opposed to chemotherapy, which merely destroys already-established cancer cells. Scientists are researching

several different enzymes for this therapy. One of these is heparanase, an enzyme that stimulates cell migration[5]. Scientists are also experimenting with a variety of tyrosine kinases that, when mutated, allow unrestricted growth in cancer cells. Of particular note is the recently released drug Gleevec, which targets tyrosine kinase BCR-Abl and is showing positive results in treating leukemia with minimal adverse effects[6]. The success of Gleevec is demonstrative of the power of enzyme inhibitor–based cancer treatment, and many researchers believe the combined power of several enzyme restriction drugs is the next step in cancer treatment. These drugs have the ability to fully restrict tumor growth while allowing patients to maintain a quality of life that is much higher than that of patients undergoing traditional cancer treatments.

Unfortunately, cancer is doing its part to counteract these advances in treatment. Most notably, cancer has begun utilizing the body's own defenses to form resistances to cancer treatment drugs, including enzyme inhibitors. These adaptations, dubbed "multi-drug resistance" cancers, or MDR, can arise through several different mechanisms, each requiring different treatment. The most common and widely understood of these mechanisms is the manipulation of p-glycoprotein (PGP) by cancer cells. Ironically, the body uses PGP as a means of toxin defense. PGP is most commonly expressed to protect highly susceptible areas of the body, such as the blood-brain barrier and the testes, and it functions by capturing and expelling toxins from these areas. Some forms of cancer have adapted to express high levels of PGP, which recognizes cancer-targeting drugs (both chemotherapeutic and enzyme inhibitor) as foreign, and expels them from the cancer cell, preventing effective treatment. While this adaptation may seem scary enough already, it is compounded by the fact that cancer has also been shown to increase expression of PGP after the initial round of drugs[7]. So even if there was some initial success, the drug's performance will continually decrease in MDR cancers. While PGP-mediated drug

resistance is the most common form of MDR, it is also the most treatable resistance, and can be combated through the use of PGP inhibitors. These inhibitors function precisely as their name implies: by inhibiting the function of PGP throughout the body, thereby preventing cancer cells from expunging drugs and making them susceptible to the same treatments as typical cancers. Previously, researchers criticized this method of overcoming MDR cancer, and rightly so, because delivery of inhibitors was systemic, resulting in crippled toxin defense systems throughout the body. However, recent research suggests that PGP inhibitors can be altered for both direct delivery to cancerous cells and increased cancer cell specificity[8]. When these alterations are perfected, PGP-mediated MDR will become a negligible issue in cancer treatment since it can be countered with no foreseeable side effects.

Aside from PGP-assisted resistance, the most prevalent forms of multi-drug resistance are those mediated by tumor-suppressor and oncogenic mutations. These resistances commonly operate via the same principles as PGP, by expelling cytotoxic drugs from the cancerous cell before they can cause harm. However, they are the result of mutations in a variety of different genes, which makes treatment of these various MDR mutations very difficult. So while research is being conducted on developing drugs to inhibit the protein responsible for some of the more prevalent of these mutations (namely those involving the MRP gene), the most promising option is also the most simplistic: rather than disable resistances, bypass them. Several methods are currently undergoing testing that utilize this simple concept to combat MDR cancer in vastly different ways. The first, which is being tested by various pharmaceutical companies, involves overloading tumor cells with anti-cancer (cytotoxic) drugs that are rapidly absorbed and fast acting. This process allows the drugs to act before the cancer cell can expunge a substantial amount, effectively negating the resistance mechanisms of the cell. While this method does serve

to counter MDR mechanisms, its shortcomings are the same as those of traditional cancer treatment options: the possible side effects are very detrimental. Because this method most often utilizes typical cytotoxic drugs (and at a higher dosage), the patient is exposed to the negative effects of whichever drug is being administered. Therefore, this method will remain only situationally viable until researchers can develop a sufficiently fast-acting and rapidly absorbed drug that does not pose the risks of currently available compounds.

In contrast to the above method, which utilizes traditional drugs in nontraditional doses to bypass resistance, research being led by Victor Keute and Thomas Efferth aims to use nontraditional compounds that actively bypass cancer cell resistance, rather than just overloading it. Keute and Efferth are examining the active compounds in African medicinal plants for cytotoxic effects. They have identified at least four different compounds in the benzophenone family that exhibit cytotoxic properties, and surprisingly, these compounds seem able to destroy drug-resistant cancer cells just as easily as they can destroy nonresistant cells[9]. This research is still in its infancy, so while thorough clinical trials to examine the viability and potential side effects of these compounds have not yet been conducted, the outlook of this research is very promising.

Many billions of dollars are spent annually on cancer research. Even so, chemotherapy and radiation have remained the dominant treatment options for more than six decades, in spite of their often severe side effects. These outdated methods have done their part to lower the mortality rate of cancer patients, but at an often substantial cost to their quality of life. Fortunately, recently developed enzyme inhibitor–based drugs, which show great promise in combating the disease with much less substantial side effects, seem poised to replace chemotherapy as the preferred cancer treatment option. Additionally, researchers are in the

process of developing several different methods to combat multi-drug resistance in cancer to deal with this ever-increasing complication. If proven successful, these combined options could revolutionize the world of cancer treatment, providing hope to the millions afflicted, and bringing us one step closer to removing cancer from the list of most fatal diseases worldwide.

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Notes

Topol E. Quote taken from a 2013 genetics symposium in San Diego.