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Editorial

Holistic Approaches in Oncotherapy

Immuno-Therapy: A New Frontier in Cancer Care

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Cancer and cardiovascular diseases account for a major percentage of deaths worldwide and pose the greatest threat to modern global public health. For 2015, the American Cancer Society estimated that approximately 1.66 million new cancer cases were diagnosed in the United States, and the figure goes up once the global statistics are taken into consideration. But why hasn't cancer been cured despite a four-decade "war" against the disease and the expenditure of hundreds of billions of dollars? Simply stated, it is essentially because of our lack of understanding of the basic underlying molecular mechanisms that drive it.

Early on, certain chemicals (such as nitrogen mustard – similar to mustard gas) were found to significantly reduce white blood cells. It was then thought that these chemicals may perhaps halt the growth of rapidly dividing cells, such as cancer cells. Thus, began an era of testing several chemicals to see if they could kill tumors. Chemotherapy was born! However, while at times effective, this approach does not elucidate the underlying molecular mechanisms or why it does not work universally or permanently. It must be recalled that the use of cytotoxic drugs is essentially an educated trial-and-error approach with one approved drug or a combination of a number of such drugs.

It does not rely on the deep understanding of the tumor biology nor does it consider the braiding of both normal and cancerous cells that is embedded in our genome. As a result, it has historically provided little durable benefit with tumors recurring within several months, even in the case of more accessible tumors located outside the brain; for brain tumors, the access is much more difficult because of the presence of the brain protective barriers, chief among these being the blood brain barrier, compounding the difficulties.

A Paradigm Change in Cancer Treatment

As cell biology and genetics became understood at a deeper level, newer targeted therapies have been designed to which the complementary procedures of surgery and radiotherapy were added and used either singly or in combination. It now appears that cancer is less an organ disease and more a disease of molecular mechanisms caused by the mutation of specific genes. More recently, the newly emerging "immunotherapy" has been successful in inducing long-term remissions of hard-to-treat cancers in about one-third of patients [1].

Immunotherapy had its early beginnings in 1987 when French researchers identified a new protein receptor on the surface of T-cells. They called it cytotoxic T-lymphocyte antigen 4 (CTLA-4). This was followed by James Allison's discovery in 1996, that CTL-4 puts the brakes on T-cells, preventing them from launching all-out immune attacks. He also wondered whether "blocking the blocker" (the CTLA-4 molecule) would set the immune system free to destroy cancer. The approach turned from considering immunosuppression as the focal point to manipulation of immunosuppression as the target.

He thus showed that antibodies against CTLA-4 erased tumors in mice. Then, in the mid-1990s, a biologist in Japan discovered a molecule expressed in dying T-cells, which he called "programmed death 1" (PD-1) and which he recognized as another brake on T-cells. Whilst engineered T-cells are still experimental, antibodies are slowly going mainstream. At least five major drug companies are developing antibodies such as anti–PD-1. Testing an anti–PD-1 antibody in 39 patients and five different cancers began in 2006. By 2008, doctors were jolted by what they saw: In five of the volunteers, all of them with refractory disease, tumors were shrinking, and survival in a few stretched beyond what was imagined possible.

Shortly thereafter, in 2010, Bristol-Myers Squibb, reported that patients with metastatic melanoma lived an average of 10 months on the antibody, compared with 6 months without it. It was the first time any treatment had extended life in advanced melanoma in a randomized trial. Nearly a quarter of participants survived at least 2 years. Now, with both anti–CTLA-4 and anti–PD-1 treatment options, physicians saw some tumors grow before vanishing months later. Some patients kept responding even after the antibody had been discontinued, suggesting their immune system had been fundamentally changed. However, some patients, particularly those on anti–CTLA-4, developed unnerving side effects, including inflammation of the colon or of the pituitary gland [2-6].

The year 2013 marked a turning point in the fight against cancer, as long-sought efforts to unleash the immune system against tumors were paying off, even if the future remained a question mark. The journal *Science* selected cancer immunotherapy as the *Breakthrough of the Year*. But, what is "immunotherapy"? It is the harnessing of the immune system to battle tumors. It represents an important paradigm shift in cancer treatment as it marks an entirely different way of treating cancer - by targeting the immune system, not the tumor itself.

To this day, however, it has touched only a tiny fraction of cancer patients and has helped only some of them. Examples include: a woman with a grapefruit-size tumor in her lung from melanoma, who is alive and healthy 13 years later; a 6-year-old near-death from leukemia, now in third grade who is in remission; and a man with metastatic kidney cancer whose disease continued fading away even after treatment stopped.

Notwithstanding the successes described above, it is well to keep in mind that immunotherapies do not help everyone (for example, for patients with metastatic cancer, the odds remain long). Researchers are largely clueless as to why more patients do not benefit and so they are racing to identify biomarkers that might offer answers and experimenting with ways to make therapies more potent.

Melanoma Immunotherapy with CTL-4 and PD-1 Inhibitors

In 2011, the US. Food and Drug Administration (FDA) approved Bristol-Myers Squibb's anti–CTLA-4 treatment, called *Ipilimumab* (sold as Yerzov), for metastatic melanoma. However, the cost is high as the company charges $120,000 for a course of therapy. In 2012, Suzanne Topalian of the Johns Hopkins University, and Mario Sznol of Yale University and their colleagues reported results for anti-PD-1 therapy in nearly 300 people. Tumors shrunk by about half or more in 31% of those with melanoma, 29% with kidney cancer, and 17% with lung cancer.

This was followed in 2014 by FDA's approval of *Pembrolizumab* for the treatment of late stage melanoma, a monoclonal (therapeutic) antibody that blocks the inhibitor ligand of PD-1. This receptor is responsible for inhibiting the immune response against cancer cells. Normally, this effect is necessary to avoid an inappropriate over-reaction, such as an auto-immune disease, in healthy individuals. In patients with cancer, antibody blockade against this receptor reinvigorates the immune system, allowing it to target and destroy cancer cells.

Pembrolizumab (one of a number of closely related therapies dubbed "immune checkpoint blockade") is sold under the brand name *Keytruda*. It belongs to the hot class of drugs called PD-1 inhibitors. By blocking the PD-1 protein, the therapy allows the body to make T-cells that can chase after a cancer. The treatment is also expensive (~ $150,000 a year). A combined (radiation +chemotherapy + Keytruda) treatment of melanoma cancer is also employed. Then, in the Fall of 2015, Bristol-Myers Squibb reported that of 1800 melanoma

patients treated with *Ipilimumab*, 22% were alive 3 years later and combining *Ipilimumab* and anti-PD-1 led to "deep and rapid tumor regression" in almost a third of melanoma patients. However, whereas drugs blocking the PD-1 pathway have not yet been proven to extend life, the resulting survival rates are highly encouraging [7-13].

Leukemia Immunotherapy with CAR-T Cells

Separately from the above developments and for years at the US. National Cancer Institute, Steven Rosenberg had harvested T-cells that had migrated into tumors, expanded them in the laboratory, and re-infused them into patients, saving some patients with dire prognoses. However, the technique was limited in its application as it worked only when tumor tissue could be accessed. However, with increased interest on genomic and personalized medicine, the question arose as to whether a personalized treatment involving genetically modified patient's T-cells could make them target tumor cells.

The idea had its beginning in the pioneering work of Rosenberg (2010) at the U.S. National Cancer Institute (NCI), dubbed chimeric antigen receptor (CAR-T)-therapy, who published encouraging results. Further, one group of researchers led by Carl June of the University of Pennsylvania began reporting eye-catching responses to CAR therapy: patients with pounds of leukemia that melted away. Later, in 2015, June and others and their respective teams reported that the T-cell therapy in their studies put 45 of 75 adults and children with leukemia into complete remission, although some later relapsed. CAR therapy had then become the focus of numerous clinical trials in the hope that, like the antibodies, it can target an assortment of cancers.

CAR-T therapy has now become an important treatment avenue. It is the subject of numerous clinical trials in the hope that, like the antibodies, it can target an assortment of cancers.

The CAR-T technology merges gene therapy, synthetic biology and cell biology in the laboratory. It involves the following four steps:

1. First, a batch of certain T-cells known to respond best to a given disease are extracted from the blood;
2. A custom-built virus is used to implant them with new genes;
3. Cells are created that target a molecule (CD19) that is found on the surfaces of some cancers;
4. The modified cells are then returned to the body, where their new DNA gives them a fresh set of targets to attack.

In a trial of 31 patients with acute lymphoblastic leukemia (ALL), the approach brought about a complete remission in 93% of cases, an unprecedented result. A refinement of the technique consisted in overcoming the toxic effects that the treatments can trigger. As the number of T-cells doubles, roughly every 12 hours, a runaway immune reaction called a *cytokine storm* is triggered, which can be fatal to certain patients. The biggest cytokine storms seem to come from the patients with the most advanced cancers. The solution is to give the sickest patients the lowest dose so that the T-cells multiply more slowly, reducing the chances of an immune-system overreaction.

Although the ALL results are impressive, it is difficult to expand the approach to other cancers because to prime a T-cell to attack, it needs to be given precise co-ordinates. Otherwise, it may lock onto and destroy something else in the body. Besides CD19, which is found in only a few cancers, scientists currently know of no other chemical target that is specific to cancer alone. The solution proposed by Kole Roybal (Cell, 2016) and his colleagues at the University of California, San Francisco consists in tweaking cells to attack when they sense two different target chemicals instead of one. In isolation, neither target may be unique to cancer cells - but the combination might be, which could allow the immune system to be unleashed on tumors whilst sparing healthy tissue [14].

While it is a long way from the laboratory to the clinic, engineered T-cells might be used to treat a wide range of diseases, including HIV, immune deficiencies, and autoimmune disorders. Besides the elegance of the idea of boosting the body's own defenses, the technology offers another big advantage over traditional drugs: once they have done their job, the engineered T-cells stick around in the body. That could offer protection against re-infection or the recurrence of a cancer possibly for a decade or more. Analogously, engineered B-cells could also perhaps be used to treat cancers that affect B-cells, another part of the immune system.

On August 30, 2017, in one of its News Releases, the FDA announced its approval of the CAR-T cell therapy to treat certain children and younger adults with B-cell ALL. This historic announcement has heralded the advent of the first gene therapy in the U.S; it has far reaching implications in treatments of cancer, and other serious and life-threatening diseases.

Glioblastoma Immunotherapy with Neutrophils

Glioblastoma, also known as glioblastoma multiform, is the most common primary brain tumor in adults. It remains an unmet need in oncology. Various treatments have been devised so far for primary tumors and their metastases in both cases of monotherapies or combination therapies, and for recurring tumors after treatment. Chemotherapy limitations (discussed earlier) are even more restrictive in the case of brain tumors. More effective therapies involving other options are required either in isolation or more likely in combination.

Such other options include the following: surgery, conformal radiotherapy, boron neutron therapy, intensity modulated proton beam therapy, antiangiogenic therapy, alternating electric field therapy, microRNA, adjuvant therapy, gene therapy, stem cell therapy, intra-nasal drug delivery, and immunotherapy, without neglecting palliative therapies [15-16].

An additional treatment option has recently been proposed based on results of experiments on mice. It consists in the use of neutrophils to deliver drugs to kill residual cancer cells that are responsible for recurring glioblastomas. Cell-mediated drug-delivery systems had received considerable attention for their enhanced therapeutic specificity and efficacy in cancer treatment. Being the most common type of white blood cells and a critical player in the innate immune system, neutrophils are known to be able to migrate across the blood brain barrier (BBB), deliver chemotherapeutic nanoparticles in the inflamed post-surgical tumor margin, target residual cells at these inflammation sites, and penetrate inflamed brain tumors. Loaded with cationic liposomal Paclitaxel, they suppress the recurrence of glioma in mice whose tumor had been resected surgically.

The mechanism of action is as follows: Inflammatory factors released after tumor resection guide the movement of the neutrophils into the inflamed brain, and the highly concentrated inflammatory signals in the brain trigger the release of *Paclitaxel* from the neutrophils, allowing delivery of the drug into the remaining invading tumor cells. This neutrophil-mediated delivery of drugs efficiently slows the recurrent growth of tumors, with may significantly improve survival rates, but does not completely inhibit the regrowth of tumors.

Researchers at the China Pharmaceutical University have loaded liposome capsules with the chemotherapeutic drug Paclitaxel and injected them in the blood of three mouse models of glioblastoma. The researchers showed that the neutrophil-carrying drugs were able to cross the BBB, destroy residual cancer cells, slow the growth of new tumors, and significantly increase the treated mice lifespan beyond that of controls. This research group is now proceeding with human clinical trials [15-16].

While this approach is promising, it has currently several limitations, including: the treatment did not prevent the recurrence of tumors; it has not been applied to humans; and the amount of blood needed for this type of procedure could be quite substantial. Some critics have even alleged that the mouse models used may be flawed, which may put into question the applicability of the method to humans. However, the Chinese clinical trials, if replicated, should help determine this critical point.

Neurodegenerative Disorders Immunotherapy with Neutrophils

Although additional studies are necessary to further validate this method, the strategy of using neutrophils to deliver drugs across the BBB could also be applied to neurodegenerative diseases and other inflammation-mediated disorders. Any disease that naturally attracts neutrophils could be targeted with this method [17-19].

Conclusions

Cancer immunotherapy represents an important paradigm shift in the treatment of cancer.by targeting the immune system, not the tumor itself. Its early steps began with the identification of the antigen CTLA-4 to the protein PD-1, wherein cancer patients with few

mutations in their tumors might respond better to PD-1 inhibitors. It continued with immunotherapy using T- (and B-) cells. Various types of cancer were considered (melanoma, colorectal, uterine, prostate, pancreas).

With the evolution of modern radiation therapy techniques and targeted drugs, more patients with metastatic melanoma can achieve complete and partial remissions, including remission of small brain metastases. The use of neutrophils to cross the blood brain barrier and target drugs to surgically resected tumor sites to prevent the recurrence of glioblastomas has not yet been demonstrated to be applicable to humans. It could theoretically be applied to neurodegenerative diseases and other inflammation-mediated disorders. More generally, any disease that naturally attracts neutrophils could be targeted with this method.

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