

Synthetic immunotherapy with chimeric antigen receptors

Abstract

Immunotherapy has proven successful in inducing long-term remissions of hard-to-treat cancers. The early identified protein receptor on the surface of T-cells (cytotoxic T-lymphocyte antigen 4, CTL-4) and a molecule (programmed death 1, PD-1) led to astonishing tumor shrinkage and increased survival, particularly in metastatic melanoma. Thus, anti CTL-4 and anti PD-1 have opened up new vistas in tumor treatment. Beyond that, genetically modified patients' T-cells and PD-1 molecules promise to be even more effective in specifically tailoring the treatment to the patient along the precepts of personalized medicine. This article essentially addresses the former case, or synthetic chimeric antigen receptor (CAR) therapy. Notwithstanding the successes achieved so far, CAR therapy may not benefit everyone and needs to be rendered more potent.

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Abbreviations: ALL, acute lymphoblastic lymphoma; CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; CTLA, cytotoxic T-lymphocyte antigen; DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; PD, programmed death

Introduction

In a recent article,¹ I emphasized that cancer is less an organ disease and more a disease of molecular mechanisms caused by the mutation of specific genes. I then described the newly emerging anti-cancer strategy of "immunotherapy" and its success in inducing long-term remissions of hard-to-treat cancers - currently in about one-third of patients. The article also succinctly reviewed the history of immunotherapy from its early beginnings in 1987 with the identification of a new protein receptor on the surface of T-cells (a blocker), called cytotoxic T-lymphocyte antigen 4 (CTL-4). In a twist on the technique, consisting of manipulating immunosuppression rather than strictly focusing on immunosuppression (that is, blocking the blocker), tumors in mice were erased by antibodies against CTLA-4. Separately, the discovery of the molecule programmed death-1 (PD-1), another blocker of T-cells, led to astonishing tumor shrinkage and increased survival, including more particularly in cases of metastatic melanoma. Anti-CTL-4 and anti-PD-1 have thus opened-up new vistas in tumor treatment.

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, dubbed chimeric antigen receptor (CAR-T)-therapy, which has now become an important treatment avenue. While anti-PD-1 therapy, pursued at Yale University among other institutions (Topalian and Sznol, 2012), promises to be an equally potent therapy, the focus of this article will be on CAR-therapy. CAR-therapy is now the subject of numerous clinical trials in the hope that, like the antibodies, it can target an assortment of cancers. Notwithstanding the successes achieved, it would be well to keep in mind that immunotherapy does not benefit every one and need to be rendered more potent.

The immune system response to cancer

In mounting an immune response to cancer, the body faces two major challenges: (a) It has difficulty distinguishing between normal

and cancerous cells as the latter have sprung from the former; and (b) Many cancer cells have developed various mechanisms to thwart the immune cell such as hiding from or/and even interfering with them.

As part of the innate mechanism of protecting healthy tissue, T-cells inspect cancer cells for the presence on their surface of two requisite molecules before they attack them: (a) MHC molecules (these are large protein complexes) that cradle protein fragments or antigens, which are the targets presented to the T-cells by D-(dendritic) cells; and (b) A co-stimulatory ligand that triggers the signal for the T-cells to attack. In the absence of either (a) or (b), or both, the T-cells simply move on. Thus, cancer cells can fool T-cells in two ways corresponding respectively to (a) and (b) above, namely, stop producing MHC on their surfaces or display a form of co-stimulatory ligands that act as off-switches. To overcome these two eventualities, the CAR technology (see below) has made it possible to genetically modify the T-cells in either of two ways, so that, (a) instead of the D-(dendritic cells), the T-cells could home-in directly on antigens that may be abundant on cancer cells without necessarily being presented by the MHC molecules or, else, (b) obviating altogether the need for the two-step process described earlier for attacking the cancer cells.

Evolution of immunotherapy using T-cells

Before the advent of the CAR technology, the following approaches were employed:

In the beginning (1980s)

The initial immunotherapeutic approach consisted in the following three steps: (a) Drawing T-cells from the patient; (b) multiplying them in the laboratory; and (c) infusing the expanded number of cells into the body. It helped some patients but did not work for long as the cells tended to exhaust themselves and shut down soon after delivery.

Cell turbocharging approaches (mid-1990s-early 2010)

This approach is similar to the initial one but it differs from it in one important and critical aspect, namely, the drawn T-cells are turbocharged prior to infusion into the body. Turbocharging means here is making the cells more abundant, more powerful and longer-acting than previously. To become activated, T-cells must receive signals from a different group of immune system players, the D-(dendritic) cells referred to earlier that are also isolated from each patient. They then release certain chemicals (cytokines) that boost the

immune system even further. After a few days, the T-cells quiet down allowing the body and the immune system to return to normal. Various turbocharging schemes were devised. Of particular interest is the one developed by June & Levine² at the University of Pennsylvania in their attempt to discover new HIV treatments.

Original D-cells: D-cells vary substantially in number and quality, especially in people with HIV or cancer, and may not offer the level of turbocharging required.

Synthetic D-cells: Such cells are mimicked by magnetic beads coated with two proteins that can improve the D-cells' stimulatory behavior. The result is ~ 100:1 more cells. This is the approach followed in many different research experiments and clinical trials.

Enhanced cell turbocharging approach (early 2010s)

The cells are here genetically altered so they can home in and attack certain kinds of cancer that originate in various types of white blood cells (particularly, leukemia and lymphoma).

The chimeric antigen receptor approach (Early-mid 2010s)

This technology merges gene therapy, synthetic biology and cell biology in the laboratory. It involves the following four steps : (a) First, a batch of certain T-cells known to respond best to a given disease are extracted from the blood; (b) A custom-built virus is used to implant them with new genes;³ (c) Cells are created that target a molecule (CD19) that is found on the surfaces of some cancers; and (d) The modified cells are then returned to the body, where their new DNA gives them a fresh set of targets to attack (Riddell, 2016). It has been tested in dozens of studies (~ 1,000 patients) in certain types of cancers (leukemia and lymphoma). Half or more of these patients are now living longer than expected and hundreds appear to be cancer-free.⁴

In step (b) above, several custom-built viruses could be theoretically employed. Thus, based on the well-known proclivity of HIV for infecting cells, Posey et al. [5] have used the HIV virus. The end result here is made up of two parts: (a) An antibody-like part of CAR that juts out of the cell surface to bind to the cancer antigen of choice; and (b) The rest of CAR plunges into and through the T-cell membrane to generate the proper signals, and activate the T-cells as soon as the cancer antigen is detected. They have further successfully employed it in a limited clinical trial against the surface protein CD19 (this protein is found on healthy B-cells as well as the malignant cells they might become). It was tested in cases of chronic lymphocytic leukemia (CLL) and an expanded repertoire of cancers.

Many research groups have reported excellent results in advanced cases of leukemia and lymphoma (Fred Hutchinson Cancer Research Center, Memorial Sloan Kettering Cancer Research Center, National Cancer Research Institute, Seattle Children's Hospital, University of Pennsylvania). The response rates vary by disease, age and medical condition of the patients, and the technique used. Thus, at the University of Pennsylvania, marked clinical improvement was noted in CLL cases and a 100% response rate after only one month in 90% of the children treated for acute lymphoblastic leukemia (ALL). Nonetheless, some relapses do occur and some ALL patients have died from treatment-related problems.

The results of the CAR-T therapy have been summarized in Fymat,¹ particularly in the case of acute lymphoblastic lymphoma (ALL).

Limitations, refinements, and improvements on the car-T technology

Limitations

Although the ALL results have been impressive, the technology cannot readily be expanded to other cancers because for a T-cell to be primed 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, we currently know of no other chemical target that is specific to cancer alone. Another limitation are the associated toxicities of the treatment, primarily the toxic side effects of colitis and pneumonitis.

Refinements

To overcome the limitation due to the uniqueness of CD19, Kole Roybal (Cell, 2016) and his colleagues at the University of California, San Francisco are tweaking cells to attack but only 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. A further refinement of the technique would consist in overcoming the toxic effects that the treatments can trigger. Another concerning aspect is the known fact that 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 then to give the sickest patients the lowest dose so that the T-cells multiply more slowly, reducing the chances of an immune-system overreaction. The CAR technology needs also to be extended to other types of cancer than heretofore examined, including breast and the unforgiving pancreatic cancer.

Improvements

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, offering protection against re-infection or recurrence of a cancer possibly for a decade or more. Also, CAR-T could be combined with other therapies to perhaps provide durable cures for certain types of blood cancer and, hopefully also, other kinds of tumors while also better controlling deleterious side effects some of which could be fatal. Thus, in the so-called triple-attack treatment, surgery is followed by focused radiation therapy to ablate lesions that may have metastasized, and further followed by a course of chemotherapy. One example of this approach is the case of melanoma lesions that may have metastasized to the brain. Another approach is provided by liver cancer, where a similar triple attack technique combining chemotherapy, thermal ablation, and hyperthermia provides a highly targeted, yet minimally invasive approach.

Conclusion

Beginning with the earlier discoveries of cytotoxic lymphocyte antigen-4 (CTL-4) and programmed death-1 (PD-1), immunotherapy has rapidly evolved during the past decade. With the accumulated knowledge of cancer biology and the immune response system, we have now progressed beyond the stage of merely working with what

nature offers us. We are no longer limited to the use of natural cancer biology but have progressed to the use of synthetic biology. We are able to overcome some natural limitations such as overcoming the need for MHC molecules that cradle the target antigens presented by the D-cells to the T-cells and for co-stimulatory ligands that trigger the signal for the T-cells to attack. By genetically modifying the T-cells, we can direct the T-cells to home-in directly on antigens that may be abundant on cancer cells.

The technology has however its limitations as we currently know of no other molecule than CD19 that is a specific cancer target. Another limitation is its toxic effects but we may be able in the future to attenuate if not eliminate their effects. The technology can be refined so as not to exclusively depend on the presence of CD19, and can be tailored to patients so as to avoid the deleterious effects of cytokine overproduction (or storms) that could be fatal for some.

Lastly, the technology can be improved by combining it with other complementary therapeutic approaches in a multi-prong attack (a combination of some or all of the following: surgery, radiation therapy, chemotherapy, thermal ablation). The future is very promising, indeed, and we can foresee the CAR-T approach being successfully tried in many forms of cancer.

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Conflicts of interests

The authors declare that there is no conflict of interest.

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