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T Cell Modification to Fight Cancer

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Introduction

Tumors cells are made of the normal cells, therefore their markers are similar to that of the normal cells. But these are made at much higher levels and these tumor substances can be found in blood, urine and other tissues. Tumor markers are protein and there is no universal marker for the detection of all cancer in there. This is the reason, that most of the cancer cells go undetected by the cytotoxic T-cells [1].

People with symptoms of cancer like-lump, opt for Biopsies test. These are the test which is significant to diagnose cancer. A biopsy is commonly performed if you have lump or swelling of a part. Their cells are removed and observed under the microscope. But why use these cancer detecting methods, when our own system is capable of killing cancer cells. T cells can be easily modified to increase the specificity. The T-cell modification is a type of molecular engineering to fight cancer [1]. The NK cells are also known as serial killers because these kill the cancer cells one by one. The problem that we are facing is the delivery of the t cells and it's expression in the tumor region. This can be improved by implanting the bio-engineered polymer on the surface of the T- cells designed to deliver and stimulate when place in tumor resection.

Keywords: T cell modification; Specificity; CAR T-cells; TCR cells

Objective

The main objective is to increase the specificity of the t-cells and fight against cancer, thereby making our own immune system as a sufficient one. T cell plays an important role in the *in-vivo* rejection of the tumor cells in many organisms. Many tumor antigens are recognized by the autologous T-cells are now known to the scientific community. There is a variety of mechanism involved in generating these tumor epitopes on cancer [2,3]. There are many institutions in which a number of clinical trials are done in order to know about the role of T-cell response to tumor rejection. Many experiments have been conducted so that the tumor can be detected. Recent studies showed that people with tumor have elevated levels of GPCRs (G-protein coupled receptors). GPCRs which are up-regulated in primary or metastatic cancer cells are studied under silico analysis and analyzed by the profiling data already available [2].

There are numerous methods which can help in increasing the specificity and strength of T-cells against cancer. There are naturally occurring tumor-infiltrating lymphocytes but this generation is not possible in all the individuals and till date, we have not been much successful in generating the TIL. Today genetically engineered lymphocytes are able to express highly active T-cells or chimeric antigen receptor targeting a variety of the tumor antigens [Figure 1].

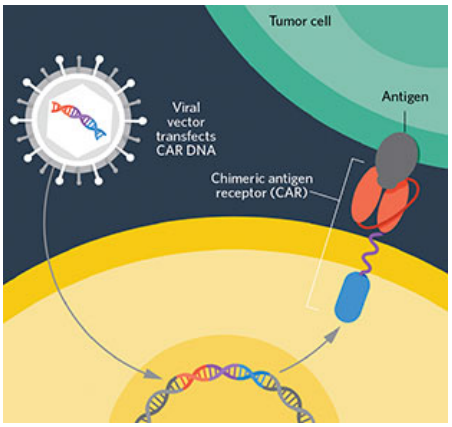

Figure 1: Chimeric antigen receptor targeting a variety of the tumor antigens.

There are T cells which have the capability of counteracting cancer proliferation like Memory and effector T cells but they fail in doing so, because of the TCR affinity of self/tumor-specific T cells [4]. Moreover, the t cells are not able to perform in the tumor microenvironment as they are suppressed by the inhibitory signals from other tumor cells. Anticancer T cells are not able to perform because of the less number in maturation, activation, differentiation, and function.

Various Approaches to Modify T Cells or Increase There Effect

First one, the immunotherapy uses the TCR-modified cells depending upon the generation of alpha and beta chains which are specific in recognizing tumor target and will also regulate the expression of these TCR molecules. There are multiple approaches that can be used to engineer the T cells. One of these approaches is to isolate the T-cells from a patient which are highly tumor-reactive and then sequence the alpha and beta chains and transfer the same sequence to the other additional T cells [3]. The most successful method that has been used was by vaccinating the mice transgenic for HLA-A2 with p^{53} peptide and subsequently, has been used to develop T cell with high affinity [Figure 2]. The ability of the engineered T cells to recognize the tumor cell depends upon the presence of the sufficient amount of alpha/beta heterodimer and their affinity to the target. And the pathways of optimizing the expression is either by the use of modified promoter or by bringing the mutation in the alpha/beta chains through changing some or all the key residues in the constant región [4].

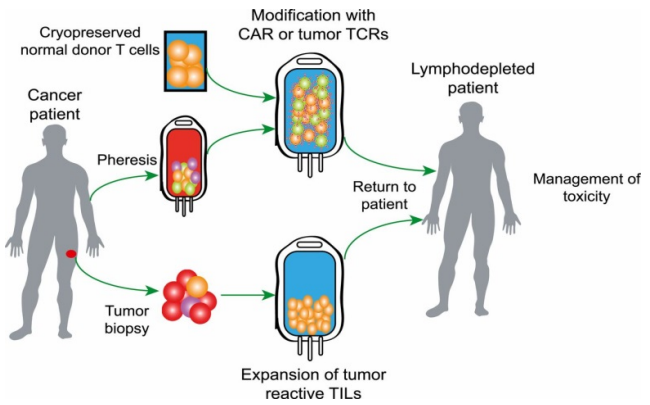

Figure 2: CAR T-cells against solid tumors.

Another fantastic approach is CAR T-cells against solid tumors. CAR T-cells are T cells which have artificially synthesized receptors, capable of recognizing specific antigens. These are modified cytotoxic T-cells and can produce interleukin 2 which helps in increasing the immune response. There are many advantages of using these CAR T-cells. Firstly, they can recognize antigen on any human leukocytes. The Human Leukocyte antigen system is a gene complex that encodes for MHC (Major Histocompatibility complex) proteins, and this expression is downregulated TCR-mediated immune response due to which many tumor cells are able to escape the response [4]. But the CAR T-cells are still able to eradicate in these escaping tumor cells. T cells are genetically modified in cancer therapy. The immune system is divided into the two: innate and adaptive immune systems. But there are ways found out by cancer cells which can escape or suppress the immune system. This, they do by downregulating the expression of the antigens thus escaping the detection.

Moreover, CAR T-cells have a wider range of the potential targets. According to the natural T cell activation CAR has got the three major domains, and they are endodomain, ectodomain and transmembrane domain. The antigen recognizing part of the CAR cells is ectodomain consisting of scFv which are derived from the light and heavy chains of an immunoglobulin, they are capable of binding to the specific antigen target. To produce the CAR T-cells, primary cells are taken from the cancer patient's peripheral blood. After the T cells are obtained, signals are sent to activate the primary T cells by using beads coated with CD3 and CD28 [5]. After the activation is done the primary T cells are redirected with CAR gene. But sometimes these cells are not safe for the body they reside in because they may attack its own cells or tissues. For this purpose, a modification is done in the T cells to enhance the safety. Strategies to improve safety include the inducing of the suicide gene or the regulated expression of the tumor targeting receptor. A suicidal gene is developed to encode human caspase 9 fused with modified human FK-binding protein. The dimerizing of the proteins by exposing cells to the permeable small synthetic molecule, which activated the human caspase 9, therefore inducing apoptosis [6]. There are numerous other ways in which local tumor immunosuppression was overcome, which were mediated by tumor stromal cells, cytokines, and negative signaling pathways [Figure 3] and the most suitable cells which are preferred for its engineering are individual $CD8^+$ T-cells which were purified before genetic engineering and its adoptive transfer demonstrates the remarkably different capacities for long-term persistence [7].

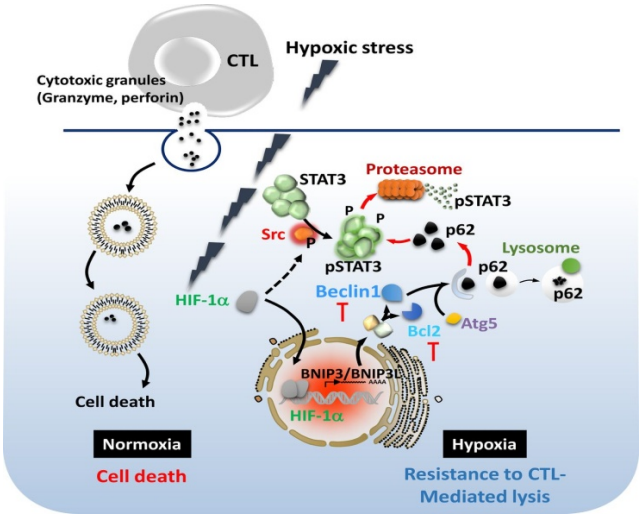

Figure 3: The expression of CTLs.

The activity of the $CD8^+$ is a powerful approach for eliminating the tumor cells. During a response to a malignancy $CD8^+$, T cells play a vital role. And these are capable of rushing through the tissues with less oxygen supply. And the studies have found that CTL immunity is regulated by the transcriptional response to the hypoxia. It is found that oxygen and Hypoxia-inducible factors affect the expression of CTLs [8]. HIFs are the transcriptional factor which is broken down under the normal oxygen tension (Oxygen tension is defined as the pressure that oxygen in a mixture of gasses would exert) by a process depending upon VHL complex. As we all know that Hypoxia is the state of low oxygen tension, it characterizes each and every site of the inflammation, tissue damage and neoplasia (presence of new abnormal growth of cells) [9]. Hypoxic environment attracts the immune cells in which these cells move against the oxygen gradient. There are several pieces of research that tells about the oxygen deprivation having an opposite effect on the innate immune response while inhibiting the adaptive immune response. Hypoxic zones in solid tumors are infiltrated by a huge number of immunosuppressive cells, tumor-associated macrophages, and T-regulatory (Treg) cells. These cells are the most widely studied immunosuppressive cell. Moreover, there is a direct link between the oxygen and cancer. Another cause of cancer is the low level of oxygen in the cells. In the newly born cells, if the oxygen levels are low, the respiration enzymes are damaged and therefore cells cannot produce energy using oxygen and become cancerous [10].

Challenges and Future Directions

There have been many advances in the development and application of immunotherapy for cancer for the past few years. The ability to rapidly get tumor-reactive T cells from the patients is a significant step by transferring its gene. There is a design of receptor to avoid autoimmunity in the case of TCRs and also increasing the efficacy against the tumor cells in the case of the CAR T-cells. T cells subsets should be genetically modified and requires the knowledge about the location and the type of malignancy being treated. There are researches going on to integrate TCR and CAR-modified T cells which will

include the immune modulating agents such as CTLA-4 or PD-1 checkpoint inhibitors [10].

Worldwide, there has been a great advancement in the therapeutic efficacy of these T cells. But still, there is a lot to discover about the CAR T-cells in solid tumors. And due to the lack of markers is likely to contribute to the "On tissue off-target" effect. The one thing which is required the most is the combinatorial effect of the CAR T cells with the other existing therapeutic approaches [11]. In the coming future, the CAR T-cells therapies would become more powerful and will potentially become a curative approach for the solid tumors.

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