The Potential of Gamma Delta T Cells in Cancer Treatment

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ABSTRACT

Cancer is still one of the major diseases in the world and 2 million new cases are estimated to appear this year. Nature has provided the body with an immune system to combat these situations. The immune system consists of numerous cells throughout the body. But the one that stands out is Gamma Delta T Cell (γδ T cell) because of its unique ability to recognize and target cancer cells independently of MHC antigen presentation. Despite being less in circulation than other lymphocytes, they exhibit various mechanisms that help them eliminate cancer cells. These cells have been stimulated and expanded using different phospho-antigens and have shown promising anti-tumor abilities. Despite their potential, clinical results show limited efficacy of these cells. However, with recent advances in genetic engineering and synthetic biology, an exciting prospect for improving cancer treatment seems like the near future.

Keywords: Gamma Delta T Cells, Immunotherapy, Cancer, Adoptive T Cell Therapy

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Introduction

Cancer is the second most prevalent disease globally and presents a major health challenge worldwide. More than 2 million cases are estimated to have appeared of cancer in 2024 [1]. Cancer immunotherapies harness the ability of the immune system to detect and destroy cancer cells. Checkpoint inhibitors and adoptive cell therapy can be utilized for cancer immunotherapies. We can use these therapies to reduce solid and hematological malignancies and change the treatment system for cancer [2]. This approach can improve the lives of many patients, but in trials, most patients do not benefit from it. That is why we need to work on more checkpoints and other factors that control T cell function to fight cancer [3]. T cells are the most important part of the immune system of our body. T cells are derived from bone marrow-derived thymic seeding progenitors. These differentiate into two main cell types: Cluster of Differentiation (CD) 4+ T cells and CD8+ T cells. Other T cell types, such as γδ T cells and Natural Killer cells (NK cells) are also present in addition to these cell types. γδ T cells exhibit specific properties that make them a suitable candidate for cancer treatment.

γδ T Cells and Their Function

γδ T cells comprise about 0.5–5% of all circulating lymphocytes. These cells were first identified following the discovery of the γ gene in 1984 [4]. These cells are unconventional T cells and function without Major histocompatibility complex (MHC)-dependent antigen presentation [5]. These cells have T-cell receptors that are formed by γ and δ chains. These are the most unique cells because they migrate to peripheral tissues rather than to the lymphoid organs. γδ T cells are equipped with both innate and adaptive properties that give them the ability to fight a lot of infections that the body faces. γδ T cells show their cytotoxic activity through their ability to express cell receptors like TCR (T-cell receptor) and NKG2D (natural killer group 2D). This cytotoxic activity is mediated by the release of mediators like perforin and granzymes [6]. Along with this, γδ T cells produce Granulysin which allows them to target and eliminate bacteria [7]. These cells have also been found to kill their target through a mechanism of antibody-dependent cellular cytotoxicity (ADCC). γδ T cells release different types of cytokines that aid their function of eliminating harmful pathogens [8].

γδ T Cell role in cancer

γδ T cells attack cancer and try to eliminate cancer in multiple ways and do this without being dependent on a single antigen. They can recognize different types of cancer cells through various membrane receptors. This ability allows them to reduce the chances of tumors being escaped from the immune system [9].

One of the methods these cells use to lyse the tumor cells is through a pathway known as a perforin-granzyme pathway. Different studies have shown that inhibiting the perforin-granzyme secretion alters the function of these cells to destroy cancerous cells [10]. γδ T cells use another mechanism of Ligands to induce cell death in the cancerous cells. They utilize the mechanisms of both TNF-related apoptosis-inducing Ligand (TRAIL) and Fas ligand (FASL). Data indicates that reducing the activity of TRAIL decreases the cytotoxicity of Gamma Delta T cells [11]. Meanwhile, Upregulation of FasL increases the ability of tumor cells to be susceptible to δ T cell lysis [12].

ADCC (Antibody-dependent cellular cytotoxicity) is another mechanism, γδ T cells utilize to eliminate cancerous cells. This process starts when the CD16 region of γδ T cell binds with the Fc (Fragment Crystalline) region of IgG (Immunoglobulin G). After binding, these cells directly start their cytotoxic effect that causes cell death, or they could cause other functions such as secretion of Interferon-gamma (IFN-γ) [13, 14]. γδ T cells secrete IFN-γ (Interferon) and TNF-α (Tumor Necrosis Factor-alpha) that alter the growth of tumor cells by increasing immunity against these types of cells and inhibit the angiogenesis of cancerous cells [15].

Engineering γδ T Cells for Cancer

Gamma delta cells have been explored for treating cancerous cells. There are two main strategies used for that purpose. One is to stimulate these cells inside the organisms by administration of compounds. Another method implies sourcing the cells by culturing and administering them to the patients [16]. This method is called adoptive T-cell transfer.

For in-vivo method, different synthetic compounds are used, to stimulate γδ T Cells inside the body. These compounds are mostly phospho-antigens and nitrogen-containing bisphosphonates (N-bis). Once stimulated, these cells begin to release cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α). This increases the cytotoxicity activity of these cells, helping them eliminate different tumor cells [17]. The most used compounds for stimulating these cells are zoledronic acid (Zol), Pamidronate (PAM), and Bromohydrin Pyrophosphate (BrHPP). But the most potent of all of these is Zol, which is commonly used for bone cancer treatment [18].

The second method starts by isolating γδ T cells from Peripheral blood cells. These cells are expanded ex-vivo using phospho-antigens or N-bis compounds and then administered to the patient. These phospho-antigens contain a hydrophobic alkyl portion linked to a polar group with phosphates that T cells can recognize. These cells then activate themselves in a TCR-dependent manner [19]. On the other hand, Bisphosphonates inhibit the farnesyl pyrophosphate synthase (FPPS) enzyme, which causes prenyl pyrophosphate metabolites like isopentenyl pyrophosphate (IPP) and geranyl pyrophosphate (GPP) to build up. These metabolites bind to the B7-family-related molecule from the Ig-superfamily, known as Butyrophilin 3A1 (BTN3A1) [20]. γδ T cells detect this binding through TCR at their surface, which triggers these cells to start proliferation and other effector functions [21]. The most effective phospho-antigens used for this method are IPP and (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP).

Some other substances can be used to alter the profile of Gamma Delta Cells. Cytokines like Interleukins and vitamin C enable the ability of these cells to proliferate and show cytotoxic activity. Also, Monoclonal antibodies (mAb) can be used which help direct the response of these cells towards the specific tumor cells [22].

Advancements and Challenges

Developments in genetic engineering have led to the development of αβ T cells that are helpful in cancer treatment. These cells are modified and encoded with Chimeric Antigen Receptors, also known as CAR-T cells. They present specific molecules that help them target tumor cells [23]. γδ T cells with CAR construct could increase their anti-tumor activity two-fold. Studies showed that these CAR-transduced cells had increased toxicity tumors [24]. Another promising approach is to alter αβ T cells through the introduction of high-affinity Vγ9Vδ2 T cell receptors (TCRs). These αβ T cells have defined γδ TCRs and are called TEGs [25]. This strategy uses CD8 and CD4 αβ T cells, enabling CD4 T cells to start helper functions. Meanwhile, natural Killer cells can also be transduced with high affinity γδ TCRs [26].

Many efforts have been made to design these cells, but achieving a clinically high number of results has been difficult. Despite having such great potential, these cells only show a 21% response rate in clinical trials [16]. These low results could be a reduction in the quantity of these cells in peripheral blood, because of infusion of these stimulants. Another big problem in developing better immunotherapies is the characteristics of these cells to act as tumor growth promotors. These cells can also secrete IL-17 and promote tumor angiogenesis [16]. These cells can change their function depending on the cytokines present in tumor micro-environments (TME), such as anti-tumor or pro-tumor function. If we can maintain perfect TME for Cytokines, we can increase the effect of these cells.

Conclusion

γδ T cells' unique ability to find and eliminate tumor cells independent of MHC antigen presentation makes them suitable for cancer treatment. However, the recent clinical results didn't show great results. We must develop T cells with enhanced activity and sensitivity to cancerous cells. However, maintaining Specific TME is challenging because, in some cases, these could act as pro-tumor cells. If we can overcome these challenges, we could help treat this disease or limit it to some extent. With new expansion strategies and the development of genetic engineering, we can make these cells a potential agent for treating cancer.

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