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Role of Immunity in Spontaneous Cure of Cancer

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ABSTRACT

This review article provides a brief overview of recent developments in a particular topic. In general, this article summarizes the current knowledge on the subject. This provides the reader with an understanding of the subject by discussing the results of a recent research paper.

Interestingly, some cancers have a particular tendency to regress spontaneously. There are several examples of such referrals. Among them, metastatic melanoma (MM), leukemia, lung cancer, and Merkel cell carcinoma deserve special mention. MM is fascinating because it can regress in the final stage of the disease. [42] The significant contribution of host immunity to early tumor genesis has recently been recognized due to our better understanding of the molecular pathways that regulate tumor cell biology and tumor-lymphocyte interactions. [3]

Targeted therapies designed to target oncogenic pathways in tumor cells may also up-regulate the endogenous immune response and tumor microenvironment. [3]Identifying T-cell inhibitory signals has led to the development of immune checkpoint inhibitors, which specifically impede the inhibition of immune effectors, amplifying and potentially expanding the pre-existing immune response against cancer. [3] This immunity against cancer can be enhanced through immunotherapies, mainly in vaccines, which stimulate natural T lymphocyte clones that specifically recognize tumor antigens. [3] Consequently, a promising anticancer therapy will aim to activate patients' natural anticancer immunity, either to eliminate residual tumor cells or to extend the dormancy period in metastatic tumor cells. Such endogenous cancer immunity plays an essential role in controlling the balance between dormant tumor cells and tumor leakage and in limiting metastasis. [3]

Malignant melanoma (MM) is the most aggressive and difficult-to-treat form of skin cancer. It is estimated that up to 90% of deaths from skin tumors are due to this malignancy. [8] Regression is more

common in melanoma than in other types of tumors; it would be six times higher than in other malignant tumors. Up to 50% of primary MM undergo spontaneous regression. However, spontaneous regression of the metastatic form of the tumor is a rare phenomenon observed in only 0.23% of cases. [8]The most frequently mentioned factors leading to spontaneous regression of MM are surgical trauma, infection, vaccination (BCG and rabies vaccines), and immunological factors. Other well-documented conditions associated with the regression of metastatic MM are blood transfusion and various endocrine factors. [8]

Among the New Age methods, auto fiction, alternative gene therapy, combined bacteriolytic therapy, and enzyme-prodrug therapy targeting bacteria are some of the potential cancer treatment modalities that use microorganisms. There is an interconnection between microorganisms, the response of the immune system, and possible mechanisms involved in spontaneous tumor regression. [33] The role of NK cells evolves with tumor progression. It offers new opportunities to manipulate NK cell function to improve response rates to cancer immunotherapy in a broader range of cancers. [23]

Self-recognition of missing target cells. Signaling from activating and inhibitory receptors regulates the activation of natural killer (NK) cells. Stressed cells, such as tumor cells, lose their MHC class I molecules, a ligand for inhibitory receptors on NK cells. At the same time, they acquire stress-associated molecules that act as ligands for receptor activation. Thus, the absence of inhibitory signaling combined with the induction of activating signaling shifts the balance towards the activation of NK cells, leading to the secretion of cytokines and the destruction of tumor cells.

Keywords: Immune cells, Cancer cells, Killer cells, Immune activation, Immune suppression, Surveillance, NK cells, T cells, Phagocytosis, Immune system, Bacteria, Tumor.

Introduction:

Immunotherapy with checkpoint blockade induces rapid and long-lasting immune control of cancer in some patients, leading to a considerable change in cancer treatment. Neoantigen-specific CD8+ T cells (Fig1) are at the forefront of current immunotherapy strategies, and most drug discoveries and clinical trials revolve around exploiting these immune effectors. [55] A critical antitumor effector is natural killer (NK) cells. These innate cytotoxic lymphocytes are present in the circulation with high frequency and are identified by their excellent ability to detect and lyse spontaneously transformed or stressed cells [55] .

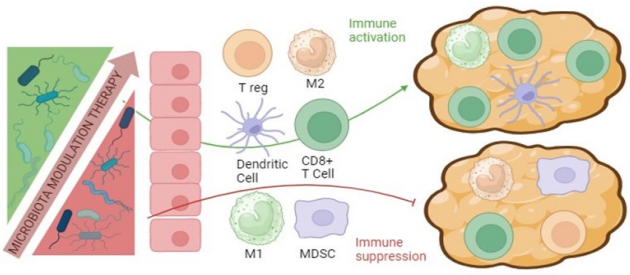

Figure 1: Shows the antitumor therapy. Immune activation and immune suppression. CD8+T immunotherapy strategies

Spontaneous regression of cancer (SR) is "when a malignant tumor partially or completely disappears

without treatment, or when there is a treatment that is considered inadequate to have a significant impact on neoplastic disease." SR, also known as Saint Peregrine's tumor, is named after a young priest named Sapsan Laziosi (1260/1345, exact date unknown), who was diagnosed with a tibial tumor. Eventually, the lump grew so large that it pierced the skin and became a severe infection. Treatment available for this condition has been limited to amputation. Historical records show that on the day of surgery, doctors found that the tumor had disappeared and never returned. [52].

Spontaneous cancer regression is an exceptional but well-documented biological event. Using mechanisms related to a deeper understanding of this phenomenon will have important preventive and therapeutic outcomes. [1] Numerous effector cells and innate and adaptive immune molecules are involved in the recognition and destruction of cancer cells in a process known as cancer immune (Fig 2) surveillance.[54] However, cancer cells evade this immune surveillance due to the growth of weakly immunogenic tumor cell variants (immunoselection) and the weakening of the immune system (immunization). [54].

Cellular barriers to tumor development in the early stages of carcinogenesis appear to correlate with stimulation of an active antitumor immune response, whereas overt tumor development appears to correlate with changes in the immunogenic properties of tumor cells. The continued success of cancer treatment depends on the use of immunogenic chemotherapy to restore the antitumor immune response. [54].

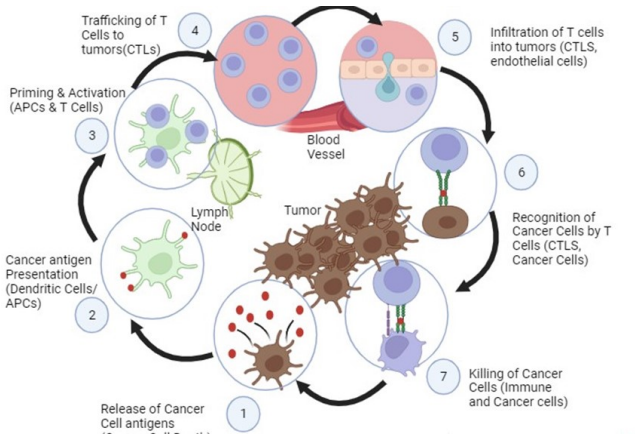

Figure 2: Numerous effector cells' innate and adaptive molecules are involved in the recognition and destruction of cancer cells in a process known as cancer immune cell surveillance.

Recent data from numerous investigations in mouse models of cancer and humans with cancer offer compelling evidence that particular innate and adaptive immune cell types, effector molecules, and pathways can sometimes collectively function as extrinsic tumor suppressor mechanisms. However, the immune system can also promote tumor progression. Together, the dual host protective and tumor-promoting actions of immunity are called cancer immunoediting. [53]

Vaccination against neoplastic cells engineered to release cytokines induces an effective protective immune response, while efficacy against established tumors is minimal. While even the most efficient cytokine-transduced cells treat only a subset of mice with micro-metastases, a phase 1 study showed that only about 10% of patients had an objective response. Combination gene therapy has been proposed to achieve greater therapeutic efficacy. (Fig 3). Several gene combinations yielded better results in the experimental model. [12].

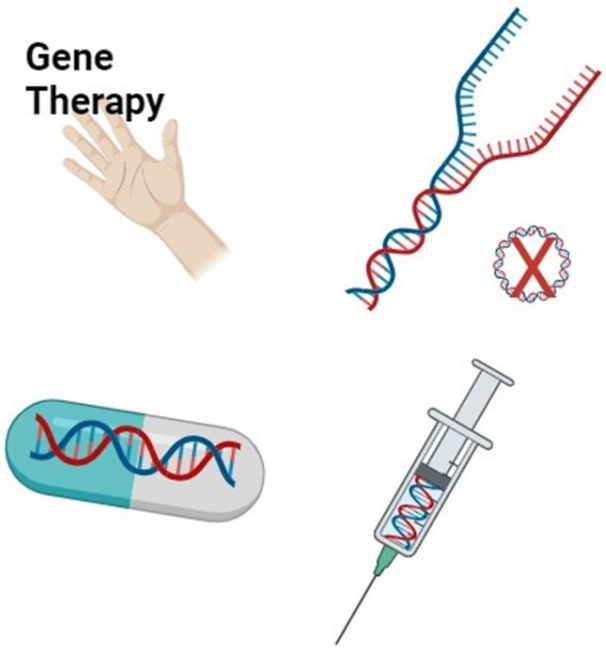

Fig 3: Combination Gene Therapy has been proposed as a method to achieve greater therapeutic efficacy

The epidermal growth factor receptor (EGFR) is overexpressed in many human cancers and often has poor outcomes. Treatment for cancers that overexpress EGFR/HER2 includes monoclonal antibody therapy (cetuximab/Trastuzumab) alone or in combination with other standard cancer treatments. Although monoclonal antibody therapy effectively treats EGFR/HER2 overexpressing tumors, its drawbacks include long-term immunodeficiency and acquired resistance to monoclonal therapy. [15].

Natural healing of cancer has been observed for hundreds or thousands of years, and after much controversy, it is now accepted as an uncontroversial fact. A review of past reports has shown that regression is usually associated with acute infection, fever, and immune stimulation. [28] In 1891, William Coley of New York Memorial Hospital developed the most effective single-agent cancer treatment made by nature, forgotten for many reasons. Cancer treatment has been standardized and improved since the days of Coley, but surprisingly, cancer patients today are no better than those treated more than 50 years ago, as researchers came out in 1999. [28]

Natural cancer regression is a phenomenon that has been described for centuries. One of the most well-known methods of spontaneous cancer regression is the use of E. coli toxins (heat-killed Streptococcus pyogenes and Serratia marcescens), which have been used to successfully treat sarcoma, carcinoma, lymphoma, myeloma, and melanoma. The use of the Bacillus CalmetteGuérin vaccine for the treatment of superficial bladder cancer in clinical practice is the most common use of microorganisms for the treatment of cancer. [34]

Substantial evidence shows that inflammation promotes oncogenesis and, occasionally, participates in cancer rejection. This paradox can be accounted for by a dynamic switch from chronic smoldering inflammation promoting cancer cell survival to florid, tissue-disruptive inflammatory reactions that trigger cancer cell destruction. Clinical and experimental observations suggest that the mechanism of this switch recapitulates the events associated with pathogen infection, which stimulate immune cells to recognize danger signals and activate immune effector functions. [34]

Generally, cancers do not have danger signals, and therefore, they cannot elicit immune solid reactions. Synthetic molecules have been developed

that mimic pathogen invasion at the tumor site. These compounds activate dendritic cells to produce proinflammatory cytokines, which in turn trigger a cytotoxic mechanism that leads to cancer death. [37] At the same time, dendritic cells take up antigens secreted by dying cancer cells, causing activation and stimulating antigen-binding T and B cells. This process significantly increases the antitumor inflammatory process. Thus, although anti-inflammatory drugs can prevent the development of some malignancies, induction of tumor antigen-specific T lymphocytes through potent immunization coupled with strong activation signals in the cancer microenvironment may provide the best strategy for treating established cancers. [37]

If a disease with a poor prognosis heals without a targeted therapeutic, many call it a miracle cure. Such is the case with the spontaneous regression (SR) of malignant neoplasms, a rare but well-documented phenomenon that finds its first mention in the Ebers Papyrus of 1550 BCE. [43] Given the challenges associated with current cancer treatment modalities, such as rapidly evolving drug resistance mechanisms, dose-limiting side effects, and a failure to eliminate cancer cells, knowledge of how a tumor heals itself would be immensely helpful in developing more effective therapeutic modalities. Although the intricate mechanisms of SR have yet to be fully elucidated, it has been shown that infection-mediated immune system activation, biopsy procedures, and disruptions of the tumor microenvironment play pivotal roles in the Self-healing of many tumors. [43] Bacterial and viral infections are exceptionally well documented in instances of SR. The conclusions drawn from these findings pave the way for new treatment strategies. Inspired by bacteria-mediated SR, Bacillus CalmetteGuérin (BCG) has been used as an approved treatment option for non-muscle invasive bladder cancer (NMIBC). Similarly, Talimogen laherparepvec (TVEC), the first oncolytic herpes simplex virus (HSV) developed, was approved by the U.S. Food and Drug Administration (FDA) for the treatment of some forms of advanced melanoma. [43]

Immunity against leukemia is essential in fighting the disease and maintaining remission in chronic myelogenous leukemia (CML) without tyrosine kinase inhibitors (TKIs). Thus, although antigen-binding immunotherapy promises to enhance immune regulation in CML, identifying targets associated with CML is required. [4] Immunotherapy has become a robust and routine treatment strategy for cancer patients. However, there are effectiveness and safety issues to address. Natural killer cells (NKs) are important innate immune cells that are gaining increasing attention for their ability to monitor immunity, regardless of their major histocompatibility complex. [8] These cells represent the first line of defense against carcinogenesis and are closely associated with cancer development. However, NK cells are functionally suppressed in the tumor microenvironment due to several immunosuppressive factors. Therefore, releasing the suppressive state of NK cells is a new project and a promising solution for immunotherapy. [8] As a result, many clinical studies on NK cell therapy are currently being conducted alone or in combination with other active ingredients.

The current state of NK cell therapy for effector-based cancer treatment and the release of NK cell inhibition in the cancer microenvironment is described in many studies. [8]

Methods:

Studies were identified by searching PubMed, Google Scholar, and Scopus, keeping the Role of Immunity in the Spontaneous Cure of Cancer, Immunity, and Cancer as the primary search words. In this systematic review, we wanted to include all published studies that provide results of Immunity of Cancer patients, whether direct antibody formation or because of microorganisms and inflammation induced by infection, vaccine, other medication, or following surgery. For inclusion into the systematic review papers, therefore, the following criteria had to be met: Study subjects had to be recruited at the hospital level (i.e., not population-based) to make them representative of the underlying hospital or hospital-based research and less susceptible to selection bias. Different designs were included to examine different aspects of Immunology about the cure of Cancer. Studies with case-control designs in a short time frame give indications of causality and longitudinal designs because they show the results of long-term exposure to Cancer on immunological function with the correct time and the sequence of exposure and outcome.

Cross-sectional studies were included to determine the association between Cancer and immunity response. Laboratory and hospital-based evidence of the Role of Immunity in the complete cure of Cancer in all age groups is available globally. To explore the biological plausibility of Immunity suppression or complete disappearance of Cancer, experimental studies on animals and histopathological studies on young children and young adults were included to determine the mechanism of action of Natural Killers (NK) in fighting against the cancer cells and killing them ultimately having searching words like T lymphocytes, immune response, inflammatory reaction, microorganism, vaccine reaction and effects of medicines were included, as were studies of the prevalence of Cancer in patients having the family history. The titles and abstracts of all articles identified by the search were screened, and potentially relevant articles were retrieved and assessed according to the abovementioned criteria. A meticulous search for articles on the Role of Immunity in the spontaneous cure of Cancer started in August 2021.

Results:

Serial #	Study	Objective	Subject	Variables	Results
1	(Tu SM, Pisters LL, et al, 2021)	To find out the drug sensitivity/ resistance and tumor immunity	Patients of Germ Cell Tumor of Testis	Testicular cancer, personalized care, targeted therapy, cancer stem cells	Germ cell tumor of the testis is a curable cancer
2	(Abdelrazeq, A. S. et al, 2007)	To identify the possible causes hypothesized by authors for the occurrence of regression.	Colorectal cancer patients	Patients, colorectal cancer, antibodies, spontaneous regression	Few cases have been reported having spontaneous regression

Table #1

3	**(Vesely, M. D et al, 2011)**	**To study the immunity of cancer for rational design of immunotherapies against cancer**	**Experimental mouse and clinical humans**	**Immuno- surveillance, immunotherapy, inflammation, immunosuppression, Immunoediting.**	**There is an immunosuppressive and immunoediting response**
4	(Vernon, L. F, et al 2018)	To explore modern immunotherapy	Cancer patients with spontaneous regression of tumor	Cancer, fever, infection, immunotherapy, cytokines	Innate immune cell therapy has shown potent antitumor activity against hematological malignancies including osteosarcoma and some solid tumors.
5	(Curiel, T. J, et al, 2007)	Find ways to boost immunity in cancer patients in the fight against cancer.	Cancer patients	Immune response, battle, tumor, novel anticancer treatment.	The new paradigm predicts that reducing tumor-induced immunosuppression will be of clinical benefit.
6	(Dobosz, P., et al, 2019)	Track cancer immunotherapy from known origins to recent events.	Experimental animals and humans	Immunotherapy, vaccine, oncolytic viruses, cancer vaccine,	The successful development of novel checkpoint inhibitors, CAR T cells, and oncolytic viruses, and the pace of these advances are the greatest promises for the future of cancer therapy.
7	(Jessy T et al, 2011)	To explore the history of immunostimulation and the role of innate immunity in inducing a cure even in advanced stages of malignancy.	Patients and experimental animals.	Acute infection, Cancer, fever, immunostimulation, spontaneous regression, Coley's toxins.	The value of Coley's observations is that many of the patients who received his treatment lived their entire lives without cancer instead of surviving a few more years with the cancer.

8	(Kucerova, P, et al 2016).	Describe the relationship between the microorganism, the response of the immune system, and possible mechanisms involved in spontaneous tumor regression.	Experimental animals and patients	Bacillus CalmetteGuérin vaccine, cancer, *Clostridium* spp., Coley's toxin, microorganisms, spontaneous regression, treatment	Among the new generation of methods, bactofection, alternative gene therapy, combination bacteriolytic therapy, and prodrug therapy using bacteria-targeting enzymes are some of the potential cancer treatments using microorganisms
9	(Mantovani, et al, 2008)	Inflammation promotes tumor formation and is sometimes involved in cancer rejection. This paradox can be explained by a dynamic shift from chronic inflammation that promotes the survival of cancer cells to a vivid tissue-damaging inflammatory response that triggers the destruction of cancer cells.	Animals and cancer patients	Microorganisms, inflammation, oncogenesis, tumor, antigen,	Although anti-inflammatory drugs can prevent the development of some malignant diseases, the induction of tumor antigen-specific T cells through active immunization, combined with strong activation signals in the cancer microenvironment, may provide a better strategy for treating established cancers.
10	(Radha, G, Lopus, et al, 2021).	The purpose of this study is to elucidate the current understanding of SR, explore its therapeutic implications, and suggest perspectives for the future.	Cancer patients	Coley's toxins, BCG vaccine, Immune cells, macrophages, dendritic cells, tumor immunology, oncolytic virus.	The occurrence of spontaneous regression has been reported in many types of cancer. Unfortunately, the SR frequency is very low. One in 60,000-1,000,000 cases of cancer. The incidence of SR was higher in melanoma, lymphoma, leukemia, neuroblastoma, renal cell carcinoma, and germ cell carcinoma. The reasons for the higher SR rates in some types of cancer are not well understood. Understanding the mechanistic aspects of SR in cancer may pave the way for innovative strategies to improve cancer outcomes.

11	(Bilich T, et al, 2018)	Identification of targets associated with CML by using mass spectrometry to identify naturally occurring class I and class II HLA-restricted peptides in primary CML samples.	Patients of chronic myeloid leukemia	Antileukemia immunity, tyrosine kinase inhibitor, chronic myeloid leukemia, cyto toxic antigen-specific T cells	This study provides a deep understanding of the native immunopeptides of CML by highlighting a panel of novel immunogenic, non-mutant, and CML-associated T-cell epitopes. These antigens aid in the development of a variety of antigen-binding therapeutic approaches that may offer deep remission, long-term TKI-free survival, or an opportunity to treat CML patients.
12	(Du N, Guo F, et al 2021)	To describe the current state of NK cell therapy for cancer therapy based on effector function and the release of the suppressed state of NK cells in the cancer microenvironment.	Cancer patients	natural killer cell, immunotherapy, cell therapy, tumor microenvironment	The therapeutic effect of NK cell therapy alone or in combination with other agents has been extensively demonstrated in numerous clinical trials, and further preclinical studies are ongoing. Therefore, there is reason to believe that NK cell therapy may be a promising cancer treatment option.

Results

The new paradigm predicts that reducing tumor-induced immunosuppression will be of clinical benefit.

CD4+CD25+Tregs are one of the tumor-induced immune evasion mechanisms that provide a prototype target for testing novel cancer treatment strategies within a novel paradigm. [12]

Cancer of germ cells of the testis was treated (Tu et al., 2021) with targeted stem cell therapy, opening a gateway for the cure of testicular cancers successfully. It is a model for further future success. The incidence of colorectal cancer is increasing even in the young population (Nasira et al., 2018). Surprisingly, cases of colorectal carcinoma have been seen with spontaneous regression of the tumor. (Abdelrazeq, A. S. et al., 2007). Immuno surveillance and cancer therapy, by producing an inflammatory response, kill the tumor cells simultaneously. Immunoactivity, whether brought by artificially or may occur spontaneously without intervention, has shown regression of tumor cells—hematological malignancies, including osteosarcoma and some solid tumors, regress by innate immunotherapy. The inflammation brings about antitumor cell activity; cytokines are released like IL15, triggering the immune response and destroying tumor cells. (Vernon, L. F, et al 2018). The most important mechanism for reducing tumors anywhere in the body is to boost the immune system by adopting different methods. Immune suppression by the tumor increases the immunity by treating the patient, which in turn increases the number of cancer-killing cells and attacks the tumor. (Curiel, T. J, et al, 2007).

Antitumor vaccines using different viruses are a hopeful and promising future endeavor that may bring about a complete cure for cancer. Currently, its trials are undertaken on animals and humans. (Dobosz, P., et al, 2019). Toxins are under trial; the idea is to stimulate the immune response. The Coley's toxin boosts the innate immunity response to produce antibodies against the tumor that attacks the cancer cells and kills them. (Jessy T et al, 2011). Use of bacteria such as Bacillus Calmette-Guérin vaccine, cancer, *Clostridium* spp., Coley's toxin, and the enzymes released by the bacteria are being used in animals and humans to see the response of these organisms on tumors. Some successful cases have been reported (Kucerova P et al. 2016). It has been observed that anti-inflammatory drugs such as Ibuprofen and Mefenamic acid have shown regression of tumors. Further research on anti-inflammatory drugs is being conducted to determine the definitive and positive outcome. (Mantovani, et al, 2008). Coley's toxins, BCG vaccine, Immune cells, macrophages, dendritic cells, tumor immunology, and oncolytic virus are used in patients with antitumor activity. (Fig 4) Unfortunately, the SR frequency is shallow. One in 60,000-1,000,000 cases of cancer. The incidence of SR was higher in melanoma, lymphoma, leukemia, neuroblastoma, renal cell carcinoma, and germ cell carcinoma. The reasons for the higher SR rates in some types of cancer are poorly understood (Radha, G Lopus et al., 2021).

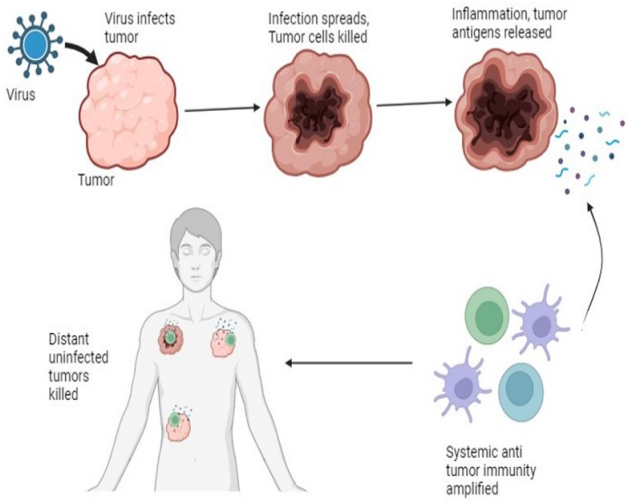

Figure 4: oncolytic viruses are used in patients

with antitumor activity.

This study aims to identify targets associated with Chronic Myeloid Leukemia (CML) using mass spectrometry to identify naturally occurring class I and II HLA-restricted peptides in primary CML samples. (Bilich T, et al, 2018) This study provides the immunopeptides of CML by highlighting a panel of novel immunogenic, non-mutant, and CML-associated T-cell epitopes. These antigens aid in the development of a variety of antigen-binding therapeutic approaches that may offer deep remission, long-term TKI-free survival, or an opportunity to treat CML patients. To describe the current state of NK cell therapy for cancer therapy based on effector function and the release of the suppressed state of NK cells in the cancer microenvironment, a study was designed using cancer patients. The therapeutic effect of NK cell therapy alone or in combination with other agents has been extensively demonstrated in numerous clinical trials, and further preclinical studies are continuing. (Du N, Guo F, et al 2021). It has been rightly emphasized that in the future, NK cell therapy will bring about a drastic change in the cure of cancer.

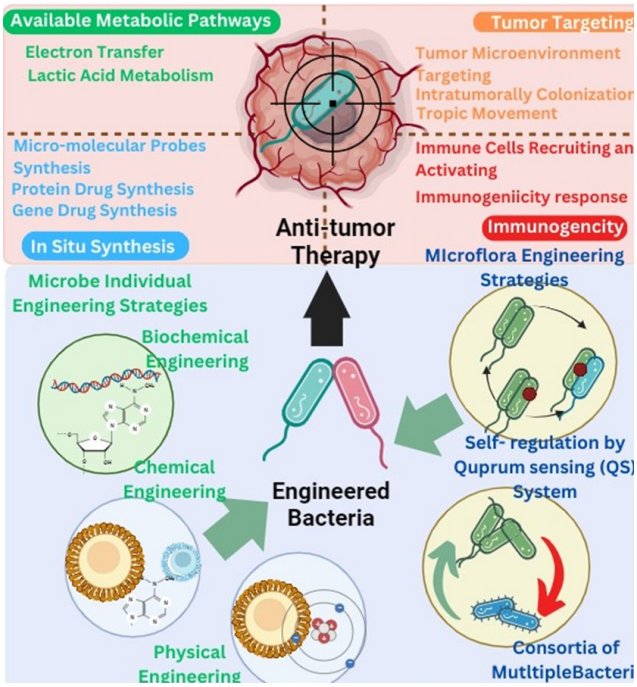

Figure 5: Vaccination against neoplastic cells engineered to release cytokines induces an effective protective immune response

Discussion:

There are two main changes in the development and progression of cancer. Normal cells transform into cells that behave malignantly, and the host's defenses cannot control these cells. Defense includes both immune and non-immune responses to cells in the wrong direction. [42] The stem cell theory of cancer is attributed to Rudolf Virchow. He was a proponent of the famous doctrine of Omnis cellula e cellula (i.e., every cell in a cell). Just as animals can only come from animals and plants can only come from plants, so cells must arise from already existing cells. However, it remains to be seen whether the cancer cells originated from normal cells and, if so, from which cells. [1] The immune system can identify and destroy new tumor cells in cancer immune surveillance, which plays an essential defense against cancer. Recently, data from numerous studies in mouse models of cancer and humans with cancer provide strong evidence that certain types of innate and adaptive immune cells, effector molecules, and pathways can sometimes collectively function as exogenous tumor suppression mechanisms.[3]

NK cells are essential immune regulatory cells that play an important role in the immune surveillance of cancer. However, the functions and properties of NK cells are impaired or altered during cancer progression. NK cells are functionally inhibited in TME due to various immunosuppressive factors, particularly TGFβ. Therefore, studies on enhancing the antitumor function of NK cells using cytokines and blocking antibodies are increasing. [6]

Technical limitations impede the development of NK cell therapies. However, technological advances have enhanced the antitumor properties of NK cell therapy by promoting the formation, reproduction, and genetic modification of NK cells in vitro. The therapeutic effect of NK cell therapy alone or in combination with other agents has been widely demonstrated in numerous clinical trials, and further preclinical studies are ongoing. Therefore, there is reason to believe that NK cell therapy may be a promising cancer treatment option. [6]

Despite abundant research, the exact role of the host immune system in cancer remains unclear. Some immune responses (specific and non-specific stimulated cytotoxic T cells and macrophages, NK cells, and cytotoxic antibodies) inhibit the growth of cancer cells or destroy cancer cells. Even (Alexander, 1972; Bean, 1981; Keller & Jones, 1971; Sullivan et al., 1980). In contrast, other specific and non-specific immune responses can promote tumor growth and proliferation, often through the production of immunosuppressive factors by the host and tumor. [42]

Tumor transplantation into animals is usually performed in inbred lines to avoid differences in histocompatibility between the donor's cancer cells and the recipient's immune system, leading to transplant rejection (Penn, 1970). Transplantation across the histocompatibility barrier usually requires some form of immunosuppressive therapy or the use of a locally immunodeficient species, such as nude mice, which receive grafts of human neoplasms. [42]

Cancer transplantation can be viewed as a very artificial situation. Even more interesting are patients with congenital immunodeficiency, patients receiving chronic immunosuppressive therapy for transplantation, and patients being treated for cancer as well as various autoimmune diseases or disorders of unknown etiology. New tumors appear in patients receiving chemotherapy. [42]

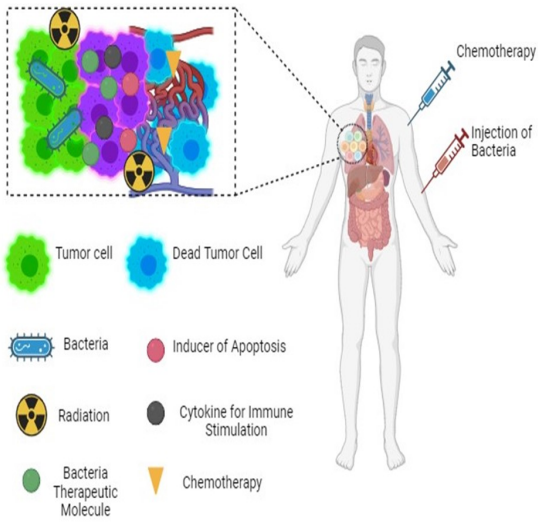

Figure 6: Multiple ways of treating cancer. The aim is to cure cancer.

Removal of carcinogens appears to be necessary, given that bladder cancer was significantly eliminated in 12 of 13 patients with bladder-to-colon urine conversion through bladder-to-colon ureter transplantation. Numerous antigens, currently unknown to us, may act as stimulants of the immune system, leading to cancer regression. (Fig6) Hormonal factors should be taken into account. [10] Interestingly, some forms of cancer are particularly susceptible to spontaneous regression. There are several examples of such mitigation. Among these, metastatic melanoma (MM), leukemia, lung cancer, and Merkel cell carcinoma deserve special mention. MM is exciting because it can regress in the later stages of the disease. In one case, the patient has suffered from MM for nearly ten years. At the time of diagnosis, she already had stage IV melanoma with a poor prognosis. However, after her febrile attack, most of her tumors disappeared,

and the rest stabilized. The frequency of SR MM is 1 in 400 patients. Although often associated with an immune response elicited by cytotoxic T cells, SR in MM can occur even without infection. [43]

Moreover, it became clear that ineffective tumor rejection was not a passive result of an insufficient number of effector cells. Recent findings show that tumors actively resist by producing immunosuppressive factors such as IL10, TGFβ, and VEGF. These and other tumor-induced immunosuppressive mechanisms will likely arise as the immune system's efforts to clear out abnormal tumor tissue simultaneously trigger intrinsic mechanisms that protect against autoimmunity generated by most antitumor immune responses. So, the biggest problem with tumor immunity is not that there is not a shortage of good things; it is that there are too many bad ones. This significant shift in thinking has not played a major role in the development of current strategies for oncology tumor immunity. It is not that there is not a shortage of good things. It is that there are too many bad ones. This significant shift in thinking has not played a major role in the development of current strategies for oncology. [12]

In the early stages of carcinogenesis, a cellular barrier to tumor development is associated with stimulating an active antitumor immune response. In contrast, overt tumor development appears to correlate with changes in the immunogenic properties of tumor cells. The continued success of cancer treatment depends on the use of immunogenic chemotherapy to restore the antitumor immune response. [56] Cancer immunotherapy uses the body's immune system to react to cancer cells. However, this can lead to increased immune response and immunogenicity. Selective and targeted therapies for cancer cells and tumors can pave the way for safer immunotherapy and nanotechnology-based delivery approaches that help achieve the desired outcomes in cancer treatment. [55]

A critical antitumor effector is natural killer cells (NK cells), cells that are frequently present in the circulatory system and are identified by their superior ability to recognize and lyse transformed or stressed cells spontaneously. It is a toxic congenital lymphocyte. Recent data indicate that intratumoral NK cells play a role in facilitating immunotherapy responses, and therefore, new efforts to further elucidate and target pathways that control the antitumor function of NK cells. It is being done. [24]

Conclusion:

Spontaneous regression has been reported in many types of cancer. Unfortunately, the SR frequency is shallow—one in 60,000 to 1,000,000 cancer cases. The incidence of SR was higher in melanoma, lymphoma, leukemia, neuroblastoma, renal cell carcinoma, and germ cell carcinoma. The reasons for higher SR rates in some types of cancer are not fully understood. Understanding the mechanistic aspects of SR in support may pave the way for innovative strategies to improve cancer outcomes.

The therapeutic effect of NK cell therapy alone or in combination with other agents has been extensively demonstrated in numerous clinical trials. Additional preclinical studies are ongoing. Therefore, there is reason to believe that NK cell therapy may be a promising cancer treatment option.

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