



REVIEW ARTICLE

CANCER IMMUNOTHERAPY: A PROMISING DAWN IN CANCER RESEARCH

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ABSTRACT: Cancer is an extremely proliferative illness with several causes, including aberrations in cell cycle control and apoptosis, DNA damage, an impaired repair mechanism, and so forth. Multiple kinds of immune cells, both innate and adaptive, are found in the cancer microenvironment and play a significant role in the development of the illness. The chemicals generated by inflammatory cells in the cancer microenvironment are the most crucial in establishing a link between inflammation, innate immunity, adaptive immunity, and cancer. Anti-tumorigenic and pro-tumorigenic responses in cancer may be triggered by chemicals released by immune cells. The balance between immunosuppressive and immunostimulatory signals within the inflammatory milieu plays a crucial role in tumour suppression. Immunotherapeutic strategies may be more useful in the fight against cancer. The chances for immunotherapy, both on its own and in conjunction with conventional medicines, are, nevertheless, increasing as immunobiology and cancer research continue to develop. As a result, this review makes an effort to highlight a potential and future-looking immunotherapeutic technique that may be used in conjunction with standard treatment methods.

Key Words: Cancer, Anti-tumorigenic, Pro-tumorigenic, Immunostimulatory, Immunotherapeutic technique.

INTRODUCTION:

An infection wouldn't be possible without the immune system's help. Cascade effects inhibit the immune system's innate and adaptive responses to pathogens. Specialized immune cells working in the tumour microenvironment cooperate to keep the host safe [1]. We rely heavily on our innate immunity, which helps mend damaged tissues and fight off invading pathogens. Adaptive immunity is activated when the body's innate immune system is compromised; it is based on antigen-specific receptors produced on clonally enlarged B and T cells [2]. Macrophages, fibroblasts, mast cells, dendritic cells, and leukocytes (monocytes, neutrophils), all of which recognise pathogenic determinants by PAMPs present on microbial nucleic acids, lipoproteins, and carbohydrates, are recruited by innate immunity when an infection or tissue injury is detected [3]. It uses the PRRs (both intracellular and surface-expressed) on these cells to detect intracellular damage caused by DAMPs generated by wounded tissues [4]. In addition, the activated PRRs trigger the activation of downstream transcription factors including NF- κ B, AP-1, CREB, IRF, *etc.*, which in turn attract leukocytes to the site of injury to heal the milieu surrounding the injured tissue. The activation of leukocytes results in the release of pro-inflammatory cytokines (TNF and IL1) and chemokines, which in turn trigger the downstream effector cells necessary for acute or chronic inflammation [5]. Anti-inflammatory cytokines, which are often generated after pro-inflammatory cytokines, neutralise the former's effects. Cancer immunotherapy makes advantage of inflammation's pro- and anti-tumorigenic actions. Acute inflammation is a natural part

of the host's defensive response, but chronic inflammation is a long-term process that may cause cancer [6]. Scientists have discovered that inflammation has a role in about a third of all malignancies. Considering the involvement of the immune system, inflammation and cancer are well known; yet, the relationship between the immune system and cancer in the tumour microenvironment is maintained by a disordered molecular pathway [7].

ORIGIN OF IMMUNOTHERAPY AND CANCER:

Paul Ehrlich proposed the concept of cancer immunotherapy in 1909 and showed that antibodies may kill cancer cells directly. The notion of immune surveillance was proposed by Burnet and Thomas in the 1950s, and it holds that the immune system eliminates malignant cells at the original cancer site before they can spread and cause tumours to form [8]. However, immunoeediting was originally used in the context of cancer research by Robert D. Schreiber and colleagues in 2001 to explain the phenomena where cancers are defined by the immunological milieu in which they originate. Researchers concluded that the immune response prevented both carcinogen-induced sarcomas and spontaneous epithelial malignancies [9]. In addition, they showed that IFN-, which helps to partly regulate the immunogenicity of tumour cells, is vital to the immune system's tumour suppressor action. The idea of immune surveillance to combat cancer is supported by experimental data that Schreiber's team generated. Although it was also claimed that tumours grown in the presence of a healthy immune system are less immunogenic than those grown

in an immunocompromised host, the immune system paradoxically favours the eventual development of tumours that are better able to evade the immune response [10]. The immune system employs four main tactics for eliminating tumours:

1. The immune system may remove viral burden, protecting the host against cancer caused by the virus.
2. The quick pathogen clearance and inflammatory response in the event of inflammation
3. prevents the inflammatory microenvironment from penetrating the tumour.
4. Thirdly, TAAs, or chemicals generated by stressed cells, are directly targeted by the immune system in order to eliminate malignancies.
5. Fourthly, the immune system is responsible for detecting and eliminating malignant and precancerous cells before they may do any harm [11].

Nothing in our world is flawless, and unfortunately, neither is our body's defensive system at completely eliminating cancer cells. Thus, certain tumour cells take advantage of this and evade immune monitoring to fuel cancer cell multiplication. The immune system is less likely to attack these tumours because they are less immunogenic [12].

Cancer cells are derived from normal cells that have undergone genetic and/or epigenetic changes. Whereas, knowing how cancer cells grow and spread without control and spreading to new areas are two of the most crucial aspects of cancer biology. If oncogenes control the onset of cancer, then the tumour microenvironment must play a role in the disease's development. Furthermore, the tumour microenvironment is impacted by inflammatory cells, which might alter tumour cells' capacity to metastasize. Unrestrained cell division, preset growth signals, resistance to growth inhibitors, avoidance of scheduled cell death, angiogenesis, tissue invasion, and metastasis are the six hallmarks of cancer; a seventh, cancer-related inflammation, is emerging [13].

Exogenously modified immune molecules (interferons, interleukins, and monoclonal antibodies) are being manipulated to provide a better immune response than conventional therapies like chemotherapy, radiation therapy, or both plus surgery, and immunotherapy has recently shown positive patient outcomes in a number of clinical trials [14]. Neo-adjuvant treatments include the use of immunotherapies in combination with adjuvants. These treatments either boost the functionality of certain immune cells or disable signals sent by cancer cells that dampen the body's natural defences. Treatments that stimulate the body's own immune system to attack cancer will play a crucial role in training the body to identify cancer cells as invaders. However, greater therapeutic results may be gained by concurrently targeting various immune pathways [15].

ROLE OF IMMUNE CELLS IN CANCER:

There is a significant contribution from the immune cells in the development of cancer [16]. Myeloid progenitors, which are a

kind of innate immune cell, and lymphoid progenitors, which are a type of adaptive immune cell, both play a role in either the growth of cancer or its inhibition [17]. Dendritic cells, macrophages, neutrophils, mast cells, and natural killer cells are the first line of defence against pathogens; when the microenvironment surrounding normal tissue is disrupted, these cells secrete a variety of cytokines, chemokines, growth factors, and proteases that interfere with the inflammatory cascade [18]. In addition, the tumour microenvironment elicits a response from adaptive immune cells including T-cells and B-cells, creating a conducive setting for the inflammatory response. Tumour-resident innate and adaptive immune cells use autocrine and/or paracrine mechanisms to coordinate their responses with cancer cells and the stromal cells (mesenchymal cells) around them (s). Almost seldom does the immune response to pro-inflammatory signals in an advanced tumour cause the tumour to shrink [19]. The tumour microenvironment dictates the balance between pro-tumor and anti-tumor immune responses and hence the direction in which the tumour must proceed. Tumor-associated macrophages (TAMs) and T cells make up the bulk of the immune cells in the tumour microenvironment. Tumor-associated macrophages (TAMs) are mostly responsible for the poor prognosis of cancer, since their enhanced infiltration promotes tumour development, angiogenesis, invasion, and migration. The presence of T cell receptors (TCR) allows researchers to classify mature T-cells into two main categories. There are several subsets of T cells, such as CD8+ cytotoxic T cells (Tc) and CD4+ helper T cells (Th) [20]. Among these Th cells are NK cells, Th1, Th2, Th17, and Treg cells. An increase in T cell counts may activate a greater population of Tc and Th cells, and this can improve the survival of patients with tumours including melanoma, invasive colon cancer, multiple myeloma, and pancreatic cancers. In experimental animal models, a decreased number of Tc cells involved may enhance vulnerability to spontaneous or chemical carcinogenesis. Many different kinds of T cells (including CD8+, Th1, Th2, and Th17 cells) have been linked to tumour development in cases of solid tumours. Until recently, it was believed that NK cells had no pro-tumorigenic function [21]. Treg cells, which behave in a pro-tumorigenic way by inhibiting the anti-tumor immune responses, are only one kind of TAM and lymphocyte that play a significant role in tumour growth. Inflammation caused by cancer is now regarded the seventh hallmark of cancer, and as leucocytes make up the bulk of the immune cell population, they may be a key predictor of cancer's progression. In both carcinoma-induced sarcomas and spontaneous epithelial carcinomas, leucocytes have exhibited protection against lymphocytes and IFN-, challenging the prior belief that they aid in immune surveillance to destroy the tumour [22]. One predictor of a bad prognosis in cancer is the presence of TILs with a high CD4+/CD8+ count and a high Th2/Th1 ratio, both of which are common in breast cancer. Th2 CD4+ T cells promote breast cancer progression and metastasis by directly targeting TAMs, where they generate angiogenesis and metastasis-promoting molecules. Like these immune cells, breast cancer cells release a number of cytokines and chemokines that promote tumour growth. These include IL-4, IL-6, and IL-8 as well as CXCR-4, CCL-2, and CCL-5 [23].

There are many unanswered questions about what elements influence whether a T cell will operate as an anti- or pro-tumorigenic in various tumours since its degeneration is not well understood at this time. Because of this, they are considered to be a crucial part of immunotherapeutics. The aforementioned events may be grouped under the umbrella term of "tumor-immune printing strategy" (TIPS), in which innate and adaptive immune cells (dendritic cells, macrophages, neutrophils, mast cells, natural killer cells, and lymphocytes)

infiltrate the tumour stroma and make it more favourable for tumour progression and escape from a further immune response in the tumour microenvironment [24]. This may have positive repercussions on the diagnostic and prognostic app in advanced stages of carcinoma, the tumor's contents may be determined by the immune cells that have invaded the tumour stroma, therefore identifying their function may be useful for both doctors and researchers [25].

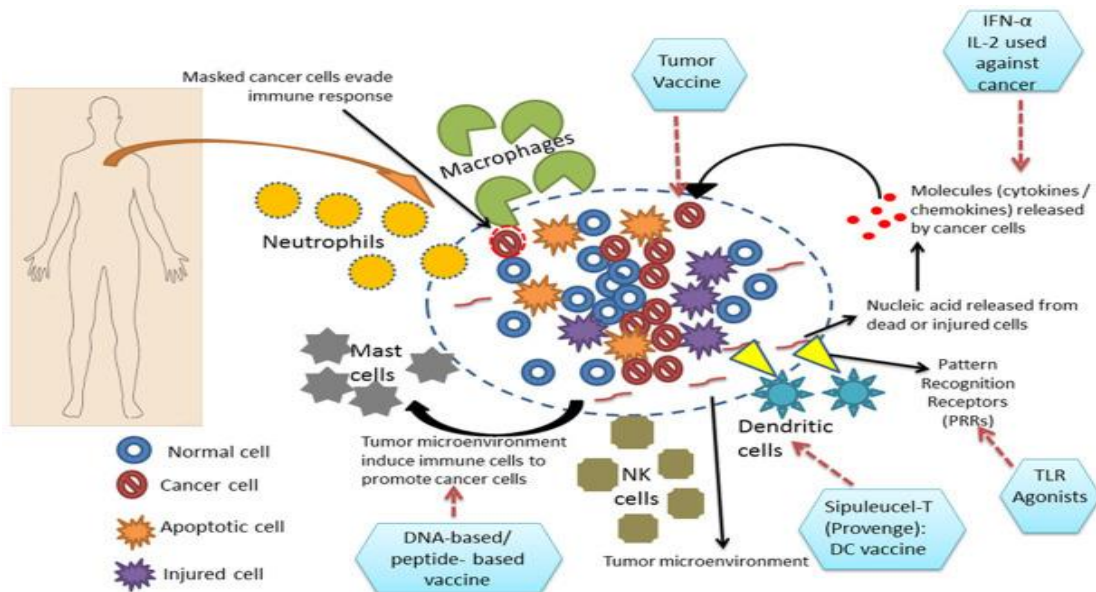


Fig. 1: The tumor-immune printing strategy (TIPS)

The tumor-immune printing strategy (TIPS) shown in this diagram illustrates the implications of immunotherapeutics in the fight against cancer by depicting the tumour microenvironment as it develops within a human body. The figure's hexagonal boxes represent the several immunotherapies utilised to attack the tumour microenvironment [26].

IMMUNE CELL INFILTRATION AND TUMOR MICROENVIRONMENT:

Recent research has shown that the immune system may play an active role in cancer progression by encouraging the development of primary tumour tissues and helping them avoid elimination via the immune selection process. The three key phases of tumour progression—elimination, equilibrium, and escape—are known to be controlled by immune surveillance, alongside host protection. Inducing a transformation from normal to transformed cells kicks off the process [27]. Cancer immune surveillance is aided by an extrinsic tumour suppressor response during the elimination phase, which rids the body of the altered cells and provides protection against the disease, which is mostly reliant on T cells. In the second phase, known as equilibrium, cancer persists owing to genetic instability and immunological response if the elimination mechanism fails to eliminate the altered cells. Cancerous states are maintained when the altered cells are able to proliferate in a milieu that promotes their survival. In an immunocompetent host, tumour

cells with less immunogenicity have a greater chance of surviving; yet, maintenance results in tumour cell escape from immunological monitoring, allowing the third phase to occur and so promoting tumour development [28]. At this point, immune-edited cells expand uncontrollably in response to immune pressure, leading to the development of invasive tumours. However, in some models, tumor-mediated active immunosuppression is found to increase the tolerance level of tumor-specific T cells, serving as a dominant immune escape mechanism. Clinically apparent malignancies acquire immune response resistance by evading adaptive immunity, demonstrating that immunoediting is a major impact of the "triple E" hypothesis (elimination, equilibrium, and escape) in cancer patients. In a certain group of patients with even immunogenic disorders like melanoma, it may facilitate the process of total inalterability of most immunotherapies and vaccines for cancer treatment. Although neoplastic cells may attract leukocytes to join inflammatory pathways that promote tumour growth, the underlying mechanisms in these tumor-mediated inflammatory responses remain elusive. Myeloid lineage innate immune cells, including TAMs and immature myeloid cells, are revealed to be inherently engaged [29].

IMMUNOTHERAPY:

Biotherapy, also known as biological therapy, is a kind of treatment for serious illnesses like cancer that makes use of the

body's own immune system. Immunological checkpoint inhibitors are employed in immunotherapy to reverse the immune tolerance adopted by certain tumour cells. Monoclonal antibodies, cancer vaccines, and non-specific immunotherapies are only few of the many kinds of immunotherapies that have seen widespread application. Nude monoclonal antibodies are one kind of monoclonal antibody used to treat cancer since they do not have any drugs or radiolabeled chemicals linked to them; they are effective on their own [30]. Some people with Chronic Lymphocytic leukaemia are helped by the use of the drug alemtuzumab. CD25 antigen is one of the molecules that it interacts to. To destroy cancer cells, chemotherapeutic medications, radiolabeled hazardous chemicals, or any agent that may kill cells, are attached to the conjugated antibodies. One such drug used to treat Hodgkin's lymphoma is Brentuximab vedotin, which works by binding to CD30 antigen. Monoclonal antibodies that can attach to two proteins at once are called bispecific. Blinatumomab, for instance, is a bispecific antibody used to treat acute lymphocytic leukaemia. One of its subunits binds to CD19, while the other attaches to CD3 [31]. Currently, monoclonal antibodies are used as immune inhibitors; for instance, ipilimumab blocks CTLA-4, and antibodies like Nivolumab (BMS-936558) and MK-3475 block PD-1 receptor and the PD-1 ligand (Merck) [32].

The immune system and tumours are getting to know one another better. A group of T cells helps T-cell activation to endure self-tolerance and bring about equilibrium. Since TLR signalling using TLR ligands is a relatively new method, it has the potential to improve the anti-tumor immune response by activating DCs and T-cells, two crucial immune cell types [33]. While TLR agonists like those used against melanoma may diminish the impact of cancer cells by inducing a Th1 antibody response and tumour antigen-specific CD8⁺ T cells in the tumour microenvironment, the response and survival of cancer patients to these treatments is dismal. Consequently, further study and development into the use of TLR agonist in cancer treatment is still needed to increase its efficacy [34].

TARGETED VACCINATION THERAPY:

Previous research has shown that the immune system does a good job of controlling tumour growth. Furthermore, adaptive immunity has been linked to promoting tumour cell "spontaneous" deterioration. Tumor-associated antigens (TAAs) are only one kind of surface antigen that the immune system recognises. Researchers and scientists have made several assertions about the efficacy of vaccine treatment, and they tend to indicate that it is more dependable than conventional remedies [35]. The immune system is essential for producing a long-lasting and efficient immune response against cancer cells once a vaccination has been administered to a patient with cancer. Tumor vaccination is another approach that shows promise. A potent and long-lasting immune response against a wide variety of tumour antigens would be desirable in a tumour vaccine. Scientists are also working on therapy-based immunizations against cancer cells in the hopes that doing so may engage the immune system to stop the growth of cancerous

cells. Anti-HER-2 vaccinations, anti-MUC-1 vaccines, anti-CEA vaccines, and anti-hTERT vaccines are only a few examples of the makeshift vaccines used to combat cancer cells. Viruses and bacteria may potentially have a role in the development of cancer [36]. To that end, immunisation may serve to prevent cancer-causing illnesses in certain circumstances. Certain High-Risk Human Papillomavirus (HR-HPV) strains are known to be carcinogenic, particularly to the cervical epithelium. Liver cancer is more common in people with chronic HBV infection, and the chronic carrier condition of Salmonella typhi has also been linked to gallbladder cancer. However, most malignancies, including those of the colon, prostate, lungs, and breasts, are not thought to be caused by infections [37]. The exact timing for the completion of the vaccination against these tumours is unknown at this time, according to doctors [38]. This vaccine's potential is high, but it will be some time before it can really be used. Immune responses may be further enhanced by mixing with other chemicals, especially adjuvants. Due to the immune system's memory cells, scientists believe the treatment might last for a considerable amount of time after it's first administered. For advanced prostate cancer, for instance, the FDA has approved Sipuleucel-T as the only vaccination for treatment, therefore ending the age of Hormonal therapy [39].

ADVANCEMENT IN IMMUNOTHERAPY: VARIETY OF CANCER TREATING VACCINES:

Scientists continuously toil away at the art of creating vaccines thought to be effective against cancer. Cancer patients' own tumour cells are used to create a tumour cell vaccine, which is then injected back into the patient after being changed to be targeted by the patient's immune system [40]. In the event that these cells or ones like them remain in the body, the immune system will attack them. Rather of using the tumour cells as a whole for their own benefit, antigen-based vaccinations stimulate the immune system by targeting specific antigens. Peptide-based vaccines are so named because they rely on TAA-derived antigenic epitopes to stimulate an immune response (antibodies, Tc-cells, and Th-cells). DNA-based vaccinations are those in which the APCs take up the DNA encoding the TAAs. These DNAs will be supplied by vectors, nanoparticles, or lipoproteins, either alone or in combination with other molecules. Nonetheless, researchers are still working out the kinks in choosing the appropriate vector given the delivery constraints. In order to stimulate an enhanced class-I and class-II immune response, dendritic cell vaccines use DCs, which in turn activates co-stimulatory molecules [41]. This immune response has the potential to counter cancer's many different entry points. Dendritic cell vaccines are among the most effective molecules used to treat cancer right now in the area of immunotherapy. Example: the dendritic cell vaccination Sipuleucel-T (Provenge), used to treat advanced prostate cancer [42].

Virotherapy is a potential immunotherapeutic technique in cancer treatment that is developing as an alternative to radiation, chemotherapy, hormonal, anti-angiogenic, and

targeted medicines. Oncolytic viruses are those that specifically attack cancer cells while avoiding normal ones. Clinical and experimental development of oncolytic viruses for cancer treatment includes herpes, measles, adenovirus, coxsackie virus, reovirus, poliovirus, poxviruses, and Newcastle disease viruses [43]. Only one oncolytic virus, a herpesvirus that has been genetically engineered, has been authorised by the FDA for the treatment of melanoma. However, clinical studies are being conducted on numerous viruses to see whether they may be used to treat cancer. When the virus infects a tumour cell, it replicates several times until the tumour cell bursts and releases chemicals, such as tumour antigens, that the immune system may use to recognise malignancy [44]. Therefore, some scientists believe tumour viruses to be an immunotherapy method. When injected into tumours, TalimogeneLairbarybvic (also known as T-VEC) releases a protein that encourages the creation of immune cells and minimises the likelihood of getting herpes. This medication was the first oncolytic virus to earn FDA clearance. It is now being tested in humans that attenuated strains of *Salmonella typhimurium* and *Clostridium novyi* may be employed as oncolytic bacteria to combat different forms of cancer [45].

COST- EFFECTIVENESS OF IMMUNOTHERAPY:

Immunotherapy has been shown to be effective for the treatment and management of many types of cancer, including melanoma, lymphoma, lung, kidney, and bladder cancers [46]. Immunotherapeutic medications have been shown by doctors to assist patients go into remission for years rather than die quickly. However, the hefty expense of immunotherapies—approximately \$100,000 per patient—remains a significant barrier to progress in this area of research. In the middle of the 1990s, the average cost of cancer immunotherapy medicines was about \$50,000 per patient. Today, that number has more than doubled to \$250,000. However, when immunotherapy costs were included in, the total cost to the patient was close to \$850,000. The majority of the pharmaceutical industry concurs that the cost of developing and manufacturing these medications in-house is prohibitive [47]. While Novartis spends around \$1 billion developing the medicine "Kymriah," the whole cost of extracting, reprogramming, and injecting the cells into each patient is less than \$60,000, much below the so-called exorbitant price tags. CAR T-cell (Chimeric Antigen Receptor (CAR) T-Cell) therapy medicine "Kymriah™ (CT019)" by Novartis is the first of its kind to be licenced by the FDA for the treatment of individuals up to the age of 25 with B-cell precursor or acute lymphoblastic leukaemia (B-ALL) [48].

The Food and Drug Administration (FDA) has authorised eight novel immunotherapy medications (MABS and NIBS) in the previous two years, but the cost is still too exorbitant for most individuals [49]. Oncologists in India are in agreement that immunotherapy is the most cost-effective option, with the first treatment costing between 1 and 1.3 lakh rupees (USD 3,000 and \$4,300) depending on the patient's weight and a second treatment typically being necessary after 21 days and lasting anywhere from 3 months to 6 months [50].

CONCLUSION:

New approaches may be created to fill in the blanks around the shady regions of Immunotherapy with the use of cost-effective and promising treatments. Furthermore, with the development of techniques and technology, immune cells may result in the creation of cost-effective immunotherapeutic strategies, which can then be utilised to create tailored medication based on patients' tumour immune profiles. Although adjuvant therapy and other vaccinations are showing efficacy in treating metastatic carcinomas, there is a vast opportunity for producing vaccines with relatively few adverse effects. It is widely anticipated that cancer immunotherapies will emerge as one of the effective treatment choices alongside more traditional procedures like surgery, radiation, and chemotherapy. This has also fuelled traditional approaches, increasing the probability of long-term tumour decrease for cancer patients and leading to effective treatment alternatives.

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