A Review on Prophylactic Immunization Against Cancer.

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ABSTRACT

As a conservative estimate 15% of cancers worldwide can be attributed to chronic infections caused by various microbial agents. A fascinating tactic with the potential to
change the face of malignancy is preventive immunisation in the context of cancer. This review provides a thorough analysis of the state-of-the-art in cancer preventive immunisation, concentrating on its causes, diagnoses, therapies, and prospects. The fundamental premise of prophylactic immunisation involves harnessing the body's own immune system to detect and eliminate malignant cells before they can manifest as clinically evident tumours. The implementation of prophylactic cancer vaccination faces notable challenges. The selection of appropriate tumour antigens that evoke strong immune responses while sparing healthy tissues is a pivotal consideration. Furthermore, establishing clinical efficacy through rigorous trials, employing relevant endpoints such as overall survival and progression-free survival, remains an ongoing challenge.

Several cancer vaccines are currently in different stages of clinical development, aim at an array of malignancies, including cervical, melanoma and lung cancer. These vaccines influence various platforms such as peptide-based, viral vector-based, cell-based, nucleic acid-based approaches, to call forth immune responses that alter the cancer type. The success of mRNA vaccines in infectious disease has paved the way for their application in cancer vaccination, offering a rapid and adaptable platform for antigen production. Combination therapies, wherein prophylactic vaccination is synergistically employed with other immunotherapies, chemotherapy and targeted agents, hold the potential to amplify the treatment outcomes

As research persists to separate out the complexities of the immune-cancer interplay, the development of effective cancer vaccines has a great probability in the ongoing battle against this formidable disease. Further research and clinical trials are imperative to advance this innovative approach and make it a practical tool to fight against cancer.

KEY WORDS

Tumor, cancer vaccines, immune system, intrinsic resistance, extrinsic resistance.

INTRODUCTION

The disorder known as cancer is defined by the body's aberrant cells growing and spreading out of control. Any section of the billions of cells that make up the human body can be the source of it. Normally, cells divide and expand in a controlled manner to produce new cells as needed by the body. New cells proliferate to take the place of aging or damaged cells. But when cancer strikes, this well-organized process breaks down, which causes an overwhelming number of aberrant or damaged cells to proliferate. Tumors are lumps of tissue made up of these cells. Cancerous tumors are indicative of malignancy, but non-cancerous (benign) tumors are not [1].

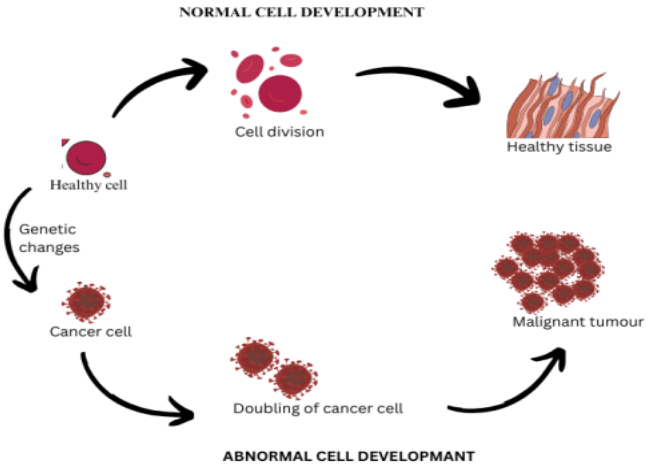

Fig.1: Normal cell development vs cancerous cell development.

Malignant tumors, another name for malignant growths, have the ability to metastasize—to go from close-by tissues to distant areas of the body. Blood malignancies such as leukemias usually do not develop into tumors, in contrast to solid tumors. However, benign tumors are not malignant and do not spread to neighbouring tissues. Benign tumors can occasionally grow fairly large, but once removed, they usually do not reoccur. Certain benign tumors can cause severe symptoms or even be fatal even though they are not cancerous, particularly if they are located in vital organs like the brain [2].

Worldwide, cancer is the second most common cause of death. As evidenced by the United States, where 1,665,540 people received cancer diagnoses, its frequency has been rising. Sadly, by 2014, 585,720 of them had passed away from the illness [3].

Every year, almost 1.2 million new instances of cancer are detected in India. The National Cancer Registry's most recent statistics indicates that one in eight Indian males and one in nine Indian women will develop cancer. Numerous factors, including age, gender, race, local environment, food, and genetics, affect the incidence and forms of cancer. Lung cancer is the most common cancer in men and is followed by malignancies of the mouth and throat. In India, breast and cervical cancer are the two most prevalent cancers detected in females [4].

Even though a lot of treatment approaches have been established for cancer, there is still no appropriate way to avoid cancer or guarantee that treatment results would be ideal for patients' quality of life. Researchers are looking into the possibility of vaccines as a cancer treatment. Cancer vaccines work by identifying particular proteins that are present on particular cancer cells, much as vaccines against other diseases. These proteins, which are referred to as antigens, activate the immune system. For example, the surface of viruses contains antigens that cause the immune system to attack them. Antigens are present in both healthy and malignant cells. Tumor-associated antigens are proteins that are either completely absent from normal cells or present in significantly lower concentrations in cancer cells. Vaccines against cancer are created to aid the immune system in identifying these antigens so that cancer cells containing them can be targeted and destroyed [5].

TYPES OF CANCER

Usually, the organs or tissues in which a cancer first appears are used to identify the disease. As an alternative, the cancer can also be classified according to the particular kind of cell that is causing it, such as squamous or epithelial cells. While there are over 200 different kinds of cancer, the majority fall into one of the following categories: [6]

1. **Carcinoma:**
   One kind of cancer called a carcinoma begins in the epithelial tissue that lines many organs, internal passageways like the oesophagus, and the skin. Organs include the skin, breasts, kidneys, liver, lungs, pancreas, prostate gland, and head and neck are all commonly affected by common carcinomas [7].
2. **Sarcoma:**
   Sarcoma is a multifaceted cancer that can appear in several body parts. It is the general name for a broad group of malignancies that originate in soft tissues (called soft tissue sarcoma in this case) as well as bones.

Particularly, soft tissue sarcoma develops in the body's encircling, supporting, and linking tissues, which include blood vessels, muscles, fat, nerves, tendons, and joint linings [8].

3. **Leukaemia:**
   White blood cells in the bone marrow are the blood cells affected by leukaemia, a type of blood cancer. The body produces blood cells in the spongy bone marrow, which is found inside some bones. Leukaemia causes aberrant blood cell counts or functions due to disruptions in blood cell synthesis. Depending on the particular blood cell impacted and how the illness progresses, there are many forms of the ailment. While some kinds develop slowly over time (chronic), others develop quickly (acute) [9].
4. **Lymphoma:**
   Cancers known as lymphomas start in the lymphatic system, which includes the many lymph nodes found all over the body, when aberrant white blood cells proliferate out of control. With the exception of skin cancers that are not melanoma, lymphomas are the sixth most common type of cancer in the world [10].
5. **Multiple Myeloma:**
   One type of cancer that starts from white blood cells called plasma cells is called multiple myeloma. These plasma cells normally generate antibodies, which are essential for fighting infections because they recognise and destroy harmful germs. On the other hand, malignant plasma cells gather in the bone marrow in multiple myeloma patients [11].
6. **Melanoma:**
   Melanoma is a kind of skin cancer that arises from mutations in melanocytes, the cells that produce pigment, which causes the cells to divide uncontrollably [12].
7. **Brain and spinal cord tumors:**
   Tumours of the brain and spinal cord are aberrant cell masses that have grown out of control within the brain or spinal cord [13].

Other types of Cancer

1. **Germ cell tumors:**
   Germ cell tumours are cellular structures derived from reproductive cells that may or may not be malignant. Most germ cell tumours begin in the ovaries or testicles. But these tumours can also develop in other body areas, such as the chest, abdomen, and brain [14].
2. **Neuroendocrine tumors:**
   Cancers known as neuroendocrine tumours develop from specialised cells known as neuroendocrine cells, which have traits in common with neuron and hormone-producing cells. These tumours are rare and can appear in different body locations [15].
3. **Carcinoid tumors:**
   One type of advancing slowly cancer that can appear anywhere in the body is called a carcinoid tumour. These tumours, which are classified as neuroendocrine tumours, usually start in the lungs or digestive tract, which includes the gastrointestinal tract, the appendix, small intestine, colon, and rectum [16].

STAGES OF CANCER

By studying data from test findings (clinical stage) or by looking at the tumour itself (pathologic stage), doctors can establish the overall cancer stage of a patient. Roman numerals are commonly used to classify the majority of malignancies with tumours into five major groupings. Although brain, lymphoma, and blood cancers have different staging schemes, all of them show the cancer's progression.

• Stage 0: Also referred to as carcinoma in situ, this condition shows only aberrant cells that have the potential to develop into cancer.
• Stage I: Known as early-stage cancer, this type of cancer is tiny and restricted to a single location.
• Stages II and III: The cancer has spread to adjacent tissues or lymph nodes and is bigger.
• Stage IV: Advanced or metastatic cancer is indicated by the spread of the disease to other bodily parts [17].

SYMPTOMS OF CANCER

Cancer is a complicated illness that frequently advances silently and shows no signs for years at a time. On the other hand, it could have observable signs that get worse quickly. Many symptoms of cancer are like those of less serious illnesses, thus having these symptoms is not always a sign of cancer. Consultation with a healthcare provider is necessary if there is a persistent alteration in your body that lasts longer than two weeks [18].

Typical early warning indicators of cancer include:

Chronic exhaustion, unexplained weight loss, persistent pain, fever, especially at night, and skin changes, such as moles altering in size or shape or developing new moles

Cancer can cause other symptoms like easy bruising or bleeding, lumps or bumps beneath the skin that don't go away, breathing problems, and trouble swallowing if treatment is not received [19].

CAUSES OF CANCER

Precancerous lesions grow to malignant tumours when healthy cells undergo a multi-stage transformation into tumour cells, which is how cancer starts. These three types of alterations result from the interaction of an individual's genetic makeup and outside influences:

• **Physical carcinogens**: ionising and ultraviolet light, for example.

• **Chemical carcinogens**: These include things like drinking water contaminated with arsenic, aflatoxin, alcohol, and tobacco smoke particles.

• **Biological carcinogens**: Emerging from infections resulting from bacteria, viruses, or parasites.

The International agency for Research on Cancer (IARC), a cancer research organisation of the World Health Organisation (WHO), maintains a list of chemicals that cause cancer. As people age, their chance of acquiring cancer rises dramatically. This is mostly because there are increasing risks linked to certain types of cancer. Together with the aging-related decline in the efficiency of cellular repair systems, there is an accumulation of danger [20].

DIAGNOSIS OF CANCER

Medical practitioners use microscopes to study cell samples in the lab. Stable cells have a regular size and well-defined structure. On the other hand, cancer cells have an uneven size distribution and an unorganised appearance. In order to diagnose cancer, physicians use a variety of techniques, one of which is making these microscope observations.

- **Physical exam.**

  A doctor may palpate your body over a physical examination to feel for any unusual bumps that might indicate cancer. The doctor also looks for anomalies that could point to the existence of cancer, like changes in colour of the skin or organ enlargement [21].

- **Laboratory tests.**

  Doctors use a variety of laboratory tests when they suspect malignancy. In order to find aberrant cells or tumour markers, these procedures include analysing collections of urine, blood, and other body fluids or tissues. This analysis aids in identifying whether an individual has the illness or a condition that is precancerous. Lab testing is useful in the following areas: establishing appropriate treatment techniques, assessing the efficacy of continuing treatment, detecting the cancer stage, and screening high-risk patients. These tests also play a critical role in the diagnosis of cancer recurrence, providing information on whether the illness has returned to its original site or whether a new malignancy has emerged [22].

- **Imaging tests.**

  Numerous imaging examinations provide information about inside bodily functions. MRI scans, which use magnets and radio waves to provide high-resolution images of organs and tissues, and CT scans, which use X-rays to produce precise cross-sectional images, are two examples of this. Although nuclear medicine scans, such as PET and scans of the bones, use radioactive elements to detect problems, mammography and MRI scans of the breast concentrate on breast health. Rapid, non-invasive techniques for evaluating internal organs and bone structures are ultrasonography and X-rays, respectively. Every test is essential for the diagnosis of various illnesses, including cancer [23].

- **Biopsy.**

  A biopsy is an essential technique that medical professionals employ to evaluate patients' bodies. In order to identify disease indicators, tissue, cells, or fluids are removed during a biopsy and examined by a medical pathologist. Providers advise this process to diagnose, track, or plan treatment for a variety of medical disorders [24].

TREATMENT FOR CANCER

Treatment for cancer entails: [25]

- **Surgery:**
  During cancer surgery, tumours are removed from the body, frequently together with surrounding healthy tissue. This age-old, multi-century-old technique is still useful for treating many forms of cancer. A surgical oncologist is an expert in this discipline. These operations can also be carried out by other specialists in surgery or cancer [26].
- **Chemotherapy:**
  Chemotherapy is a cancer treatment that works by killing cancer cells using drugs. Despite their differences, all chemotherapy medications work by preventing cancer cells from proliferating. These drugs successfully fight the illness by stopping its growth and spread within the body [27].
- **Radiation therapy:**
  High radiation doses are used in radiation therapy, commonly referred to as radiotherapy, to destroy cancer cells and shrink tumours. On the other hand, minimal radiation exposure is required for procedures such as X-rays, which enable medical professionals to view interior body parts like teeth or broken bones [28].
- **Hormone therapy:**
  One type of cancer treatment called hormone therapy stops the growth of tumours that are dependent on hormones. This strategy, sometimes referred to as endocrine therapy, hormone therapy, or hormonal therapy, attempts to reduce or stop the hormone-driven cancer's spread [29].
- **Immunotherapy:**
  As a cancer treatment, immunotherapy strengthens your body's ability to fight cancer cells. The body is protected from infections and illnesses by the immune system, which is made up of white blood cells and organs and tissues of the lymphatic system. As a type of biological therapy, immunotherapy uses materials produced from living things to treat cancer [30].
- **Stem cell transplant (bone marrow transplant):**
  For some tumours or illnesses, a bone marrow transplant (BMT) is a specialised treatment. The process involves removing bone marrow cells, also referred to as stem cells, purifying them, and then returning the cells to the patient or donor [31].

IMMUNE SYSTEM

The immune system comprises cells, chemicals, and processes designed to safeguard the skin, respiratory passages, intestinal tract, and other body regions from foreign antigens like bacteria, fungi, parasites, viruses, cancer cells, and toxins [32].

The immune system is composed of various elements, such as white blood cells (leukocytes), the spleen, bone marrow, lymphatic system, thymus, as well as the tonsils, adenoids, and appendix [33].

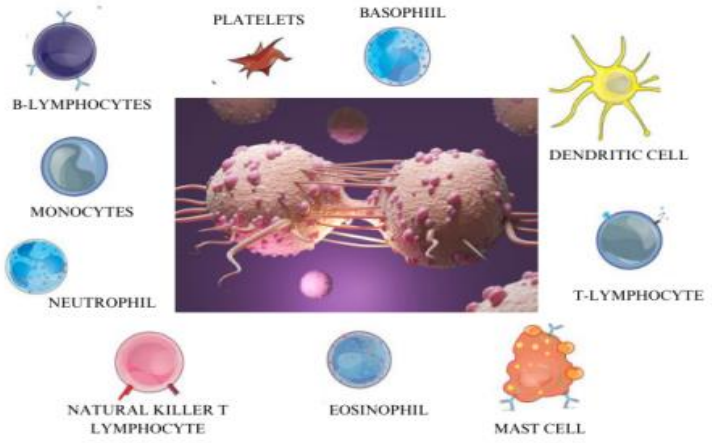

Fig.2: Tumor Immunology.

Cancer is characterized as an inflammatory disease, and within human malignancies, diverse immune system cells are present, including those from the innate immune system such as macrophages and neutrophils, along with cells linked to an adaptive immune response like T and B cells [34].

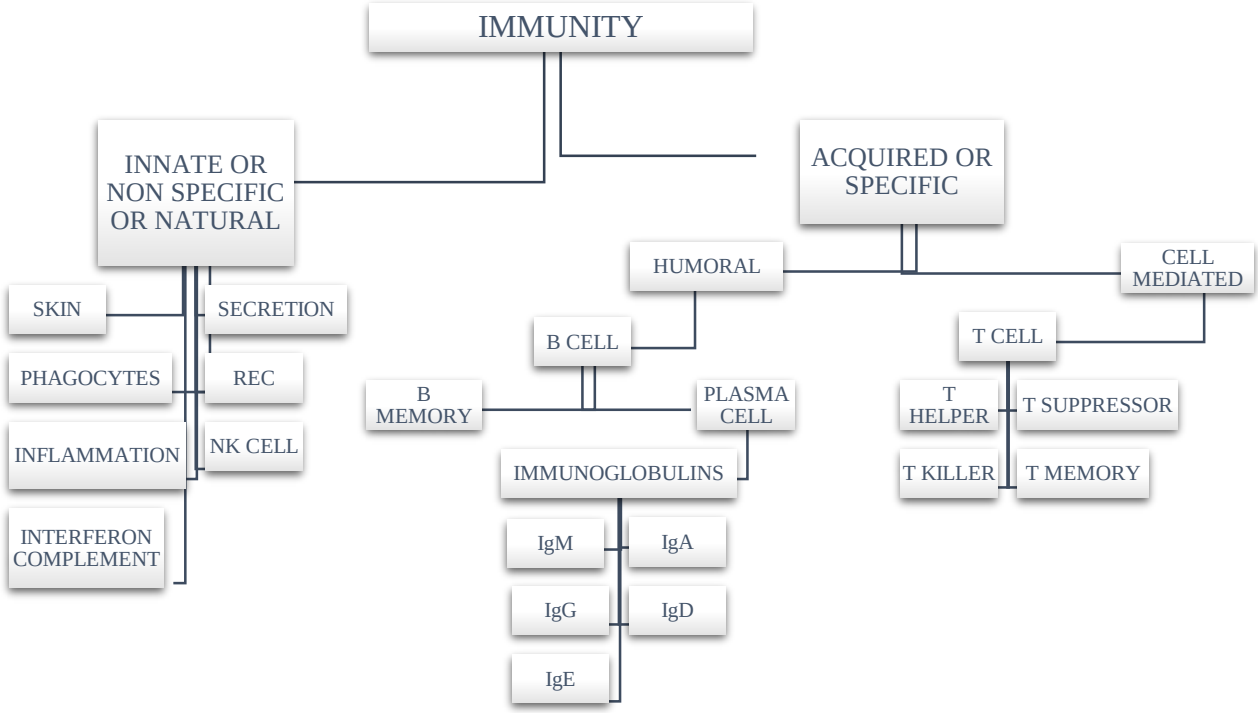

Fig.3: Classification of immune cells.

MECHANISM OF CANCER VACCINES

Cancer treatment vaccines enhance the immune system's capability to locate and eliminate antigens. Cancer cells frequently possess unique molecules called cancer-specific antigens, which healthy cells lack. Administering these molecules through a vaccine transforms them into antigens within the person's body [35].

TUMOUR ANTIGENS

Tumor cells often produce antigens, which can either be released into the bloodstream or remain on the cell surface. Any molecule that the immune system can recognize is considered an antigen. These antigens have been detected in numerous human cancers, including Burkitt lymphoma, neuroblastoma, melanoma, osteosarcoma, renal cell cancer, breast cancer, prostate cancer, lung cancer, and colon cancer. One of the immune system's crucial roles is to detect these antigens, marking them for eradication. However, the immune response to tumor antigens varies and is often insufficient to prevent tumor growth.

Tumor-associated antigens (TAAs) are mostly limited to tumor cells, whereas tumor-specific antigens (TSAs) are unique to these cells. TSAs and TAAs are typically fragments of intracellular molecules displayed on the cell surface as part of the major histocompatibility complex. However, some antigens, like Mesothelin (overexpressed in various tumor cells and normal mesothelial cells) and Claudin 18.2 (found in gastric, pancreatic, oesophageal, ovarian, and lung tumors), are selectively expressed on the surface of tumor cells and are potential targets for therapeutic interventions [36].

STIMULATION OF ANTI-TUMOUR ACTIVITY

Antigen-presenting cells (APCs), notably dendritic cells (DCs), are central in activating the immune response against tumor antigens. Immature DCs efficiently capture antigens through phagocytosis and micropinocytosis, a process further boosted by Toll-like receptor ligands in the tumor microenvironment (TME). After antigen uptake, mature DCs enhance MHC I, MHC II, and co-stimulatory molecules, then migrate to lymph nodes for T cell priming. These DCs present processed antigens to naive CD4+ and CD8+ T cells, triggering their activation and differentiation into memory and effector T cells. Activated T cells, alongside CD4+ T cells, collaborate with other immune cells, amplifying the anti-tumor T cell response. Crucially, CD8+ cytotoxic T lymphocytes (CTLs) play a pivotal role by detecting and eliminating tumor cells using mechanisms like perforin, granzymes, FasL, and cytokines such as IFN-γ and TNF-α. Cancer vaccines activate cellular immunity, initiating the cancer-immunity cycle, leading to tumor cell eradication and fostering enduring anti-tumor reactions [37].

THE BARRIERS IN VACCINE THERAPY: IMMUNE RESISTANCE

Tumor-immune evasion involves intrinsic factors related to tumor cells and external elements like tumor matrix components. These factors collectively influence the effectiveness of cancer vaccines.

TUMOUR INTRINSIC RESISTANCE

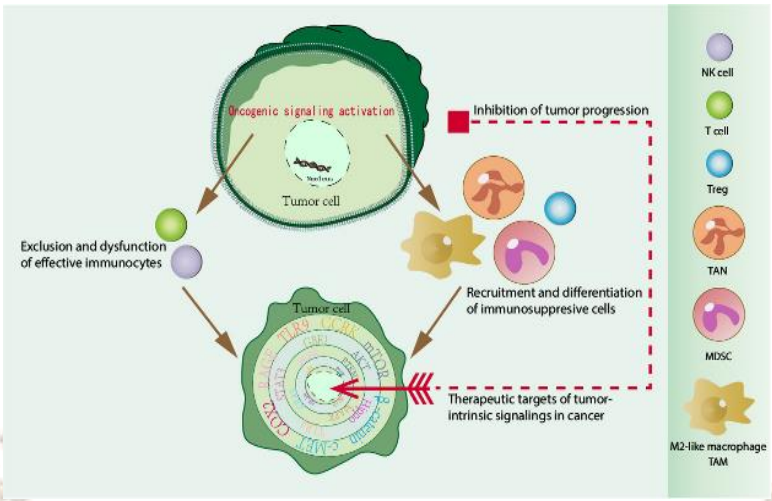

Fig.4: Tumor intrinsic resistance [38].

Targeting tumor-intrinsic signalling is a therapeutic approach for cancers. This signalling activation controls and enhances the immunosuppressive tumor microenvironment, leading to the exclusion and dysfunction of active immune cells and the recruitment and differentiation of immunosuppressive cells. Consequently, focusing on tumor-intrinsic signalling represents a promising strategy for cancer treatment [38].

TUMOUR EXTRINSIC RESISTANCE

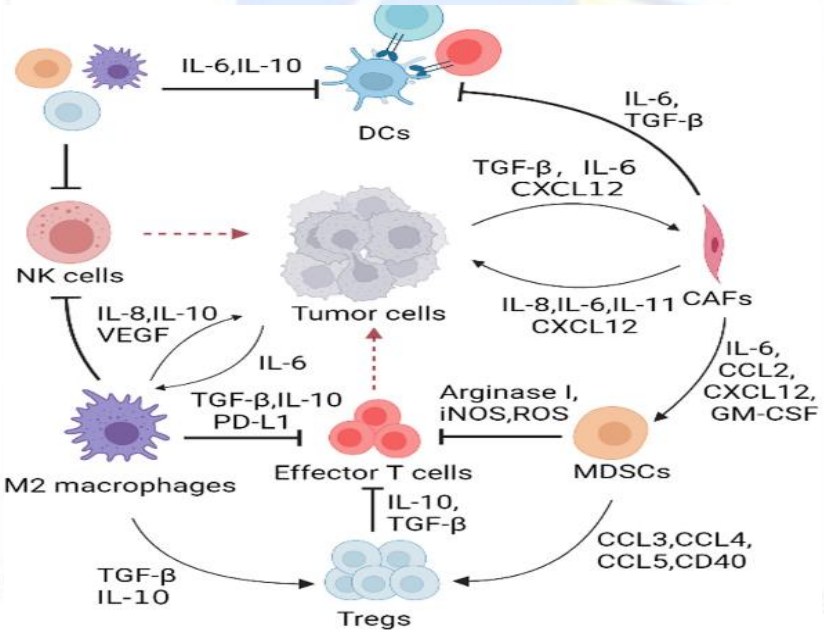

Fig.5: Tumor extrinsic resistance [39].

External resistance in tumors involves immunosuppressive cells like CAFs, MDSCs, Tregs, and M2 macrophages, along with immunosuppressive cytokines. These elements can directly or indirectly hinder the activation of effector T cells and T cells mediated by DC in the tumor microenvironment [39].

CANCER VACCINES PLATFORMS

There are four categories of cancer vaccines: cell-based, virus-based, peptide-based, and nucleic acid-based.

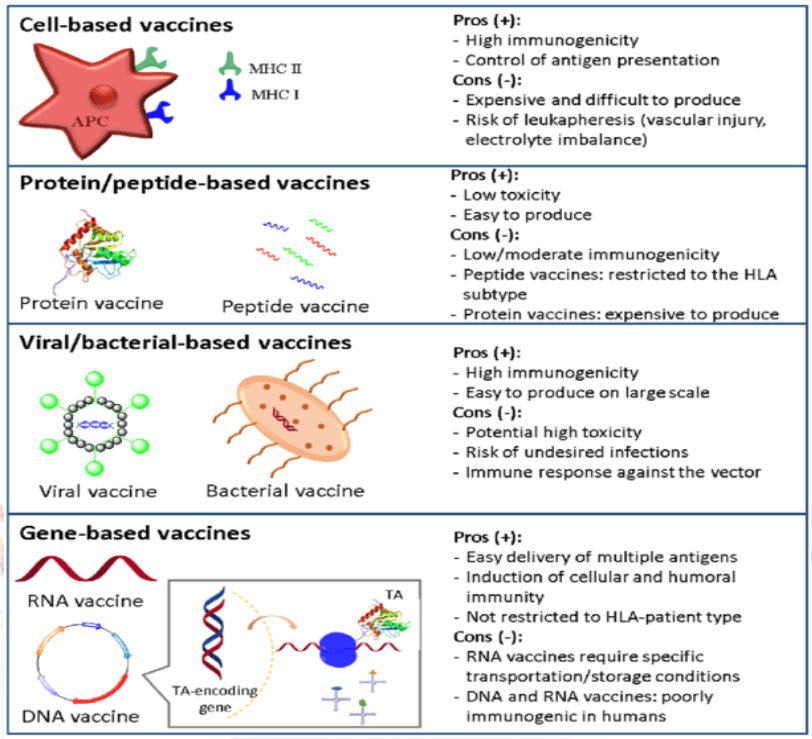

Fig.6: Types of cancer vaccines [40].

1. **CELL-BASED CANCER VACCINES:**
   Therapeutic cell-based vaccines primarily involve activating intrinsic immune cells, such as NK cells or dendritic cells, in vitro using viral peptides or viral genes. For patients with chronic HBV infection, where HBV-specific T cells are scarce, in vitro restoration of these T cells' function can be achieved through therapies with anti-PD1/PDL-1 checkpoint inhibitors. Although these therapies have shown success in specific solid malignant tumors like lung cancer, renal carcinoma, and melanoma, there is currently no available data on their effectiveness for chronic HBV [41].
2. **VIRUS-BASED CANCER VACCINES:**
   Virus-based vaccines play a pivotal role in eliciting innate and adaptive immune responses against cancer-related viruses. These vaccines exist in three forms: inactivated, live attenuated, and subunit vaccines. While inactivated whole virus vaccines have proven effective against diseases like Covid-19 and Ebola, their application in virus-related cancers faces challenges in production and safety. Bioengineering technologies, such as virus-like particles, are increasingly utilized in cancer treatment. Oncolytic viruses like herpes simplex, adenovirus, measles, and vaccinia are emerging as potent immunotherapies. They selectively eliminate tumor cells, stimulate immune responses, and release tumor-associated antigens (TAAs). T-VEC, a recombinant herpes simplex virus, has shown promising outcomes in clinical trials. Adenovirus, known for its ease of manipulation and wide host cell tropism, serves as a potential vaccine platform, functioning as non-replicating vectors and oncolytic agents. Additionally, other vectors like vaccinia virus, lentivirus, and adeno-associated virus are utilized, with lentivirus and adeno-associated virus ensuring stable and long-term transgene expression in non-dividing cells. These advancements underscore the encouraging prospects of virus-based cancer vaccines and immunotherapies [42].
3. **PEPTIDE-BASED CANCER VACCINES:**
   Peptide-based cancer vaccines utilize tumor-specific antigens to activate the immune system, initiating the destruction of tumor cells. These vaccines consist of 20-30 amino acid peptides containing specific epitopes, encouraging immunogenic responses. Short peptides (8-12 amino acids) bind to HLA class I without further processing but may induce tolerance or short-term CD8+ T cell responses. Synthetic long peptides (SLPs, 20+ amino acids) are stable and activate both CD4+ and CD8+ T cells, generating robust and enduring antitumoral immune responses. Multiepitope peptide-based vaccines, incorporating class I and class II epitopes, enhance CD4+ and CD8+ T cell activation, providing clinical advantages against tumors. Branched peptide trees with repeating sequences enhance stability and immunogenicity, as seen in

surviving-based vaccines. Personalized peptide neoantigens activate specific T cells, transforming "cold" tumors into "hot" ones, bolstering antitumor responses. Modifying peptide sequences, such as single amino acid replacements, can enhance T cell responses. Challenges remain, including limited MHC-peptide complexes and insufficient costimulatory signals in tumor cells [43].

4. NUCLEIC ACID-BASED CANCER VACCINES:

Cancer DNA vaccines and mRNA vaccines represent innovative avenues in cancer immunotherapy, utilizing genetic data to encode specific tumor antigens (TAs) and bolster the body's immune response against cancer cells. DNA vaccines consist of engineered DNA molecules encoding TAs and immunomodulatory components. To function, these vaccines must enter antigen-presenting cells (APCs), travel to the nucleus, and initiate transcription, leading to TA translation. The resulting proteins are processed either intracellularly via proteasomes or extracellularly in endosomes, yielding peptides presented on MHC I or MHC II molecules. APCs then display these epitopes to CD4+ and CD8+ T cells, as well as B cells. Despite their potential, DNA vaccines often exhibit low immunogenicity, necessitating exploration into various optimization strategies.

In contrast, mRNA vaccines are generated by in vitro transcription of template DNA, producing RNA molecules encoding specific TAs. Due to advancements in stability, structure, transfection methods, and purification techniques, mRNA vaccines have shown promise in both preclinical and clinical trials. Unlike DNA vaccines, mRNA vaccines only require crossing the cell membrane for translation, and they generally exhibit slightly higher overall immunogenicity. These vaccines utilize patient-specific TAs derived from individual tumor samples, offering a personalized approach to cancer treatment. Continuous research and optimization endeavours aim to enhance the efficacy of both DNA and mRNA vaccines, paving the way for more potent and effective cancer immunotherapies in the future [44].

APPROVED THERAPEUTIC CANCER VACCINES

TABLE 1- Cancer vaccines approved to be released in the market [45].

Formulation	Product	Company (Country)	Cancer type	Status	Completed/ terminated phase III
Dendritic cell	Provenge	Dendreon Corp. (US)	Prostate cancer	Approval (2010 US), Submission (2011 EU), III ongoing	III D9901 III D9902A III D9902B, IMPACT
Dendritic cell	DCVax-Brain	Northwest Biotherapeutics, Inc. (US)	Glioblastoma	Approval (2007 Switzerland), III ongoing	Not completed
Dendritic cell	HybriCell	Genoa Biotechnologia S.A. (Brazil)	Renal cell carcinoma, melanoma	Approval (2005 Brazil)	Not completed
Tumor cell	M-Vax™	AVAX Technologies, Inc. (US)	Melanoma	Approval (2005 Switzerland), Approval withdrawal (2002 Australia), III ongoing	III (immunopharmacology)
Protein	CIMAVaxEGF	Center of Molecular Immunology (Cuba)	Non-small cell lung cancer	Approval (2008 Cuba, Peru), III ongoing	Not completed
Peptide	Oncophage (vitespen)	Agenus, Inc. (US)	Renal cell carcinoma	Approval (2008 Russia),	III C-100-12

				Submission failure (2009 EU)	

SELECTED ONGOING CLINICAL APPLICATIONS

TABLE 2- Selected ongoing clinical application of cell-based cancer vaccines (2016 - 2021) [46].

NCT Number	Status	Conditions	Phases	Category
NCT03190265	Recruiting	Pancreatic cancer	II	Tumour cell
NCT03767582	Recruiting	Advanced pancreatic, Ductal Adenocarcinoma	I/II	Tumour cell
NCT03096093	Recruiting	Cancer, Neoplasms	I/II	Allogeneic cell
NCT04567069	Recruiting	Gastric cancer	I/II	DC
NCT03384914	Recruiting	Breast cancer	II	DC

TABLE 3- Selected ongoing clinical application of virus-based cancer vaccines (2016 - 2021) [46].

NCT Number	Status	Targeted antigens	Conditions	Phases	Category
NCT03136406	Active, not recruiting	Mutant KRAS	Pancreatic cancer	I/II	Virus vector
NCT03632941	Recruiting	HER2	Breast cancer	II	Virus vector
NCT04432597	Recruiting	PRGN-2009	HPV-associated cancer	I/II	Virus vector
NCT03113487	Recruiting	p53	Recurrent Ovarian, Primary Peritoneal, Fallopian tube Cancer	II	Virus vector
NCT03953235	Recruiting	Neoantigens	Non-Small Cell Lung Cancer, Colorectal Cancer, Pancreatic Cancer, Solid Tumour	I/II	Virus vector/ mRNA

TABLE 4- Selected ongoing clinical application of peptide-based cancer vaccines (2016 2021) [46].

NCT Number	Status	Targeted antigens	Conditions	Phases	Category
NCT04747002	Recruiting	DSP-7888	Acute Myeloid Leukaemia in Remission	II	Peptide
NCT04114825	Active, not Recruiting	RV001V	Prostate Cancer Recurrent	II	Peptide
NCT03149003	Recruiting	DSP-7888	Glioblastoma	III	Peptide
NCT04206254	Not yet Recruiting	gp96	Liver Cancer	II/III	Peptide
NCT04646005	Recruiting	ISA101b	Cervical Cancer	II	Peptide

TABLE 5- Selected ongoing clinical application of nucleic acid-based cancer vaccines (2016 - 2021) [46].

NCT Number	Status	Targeted antigens	Conditions	Phases	Category
NCT04090528	Recruiting	pTVG-HP, pTVG-AR	Prostate Cancer, Metastatic Cancer	II	DNA
NCT03502785	Active, not Recruiting	INO-9012	Urothelial Carcinoma	I/II	DNA
NCT03897881	Recruiting	Neoantigens	Melanoma	II	mRNA
NCT04163094	Recruiting	W-ova1	Ovarian Cancer	I	mRNA
NCT03468244	Recruiting	Neoantigens	Digestive System Cancer	Not Applicable	mRNA

CONCLUSION

In summary, cancer is an intricate and deadly illness brought on by the body's aberrant cells growing out of control. Because of its heterogeneous nature and origin in different tissues, it requires a multimodal approach to diagnosis and treatment. A promising new direction in cancer immunotherapy is the use of cancer vaccines, which try to activate the immune system to identify and eliminate cancer cells.

The network of cells and processes that makes up the immune system is essential to the mechanisms underlying cancer vaccines. Cancer vaccines improve the immune system's capacity to recognise and target antigens specific to cancer by inducing anti-tumor action. These specific antigens found in tumour cells serve as the foundation for a few cancer vaccine platforms, such as vaccines based on peptides, viruses, cells, or nucleic acids.

However, both internal and extrinsic immune resistance mechanisms inside the tumour microenvironment impede the effectiveness of cancer vaccines. For cancer vaccination therapies to be effective, these obstacles must be removed. Notwithstanding the difficulties, there is promise for more potent and individualised cancer immunotherapies in the future because to continuing research and developments in vaccination technology, particularly in the areas of mRNA and DNA vaccines.

Understanding the intricacy of the illness, investigating cutting-edge vaccination platforms, and addressing immune resistance mechanisms are critical stages in the fight against cancer that will improve results and provide relief to millions of people worldwide.

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