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A Review Immuno-Oncology Agents for Cancer Therapy

Unnati Adhate[1], Rushikesh Bachhav[2]

[1]Department of Pharmaceutical Quality Assurance,
[2]Department of Pharmacology,
[1, 2]R. G. Sakal College of Pharmacy, Anjaneri, Nashik, Maharashtra, India

ABSTRACT

Until recently, cancer treatment had four main types of treatment: surgery, radiotherapy, chemotherapy and targeted therapies. Over the past decade, immuno-oncology (IO) has emerged as a new and important alternative to cancer treatment by promoting the immune system to kill cancer cells. This newly developed cancer treatment is growing rapidly, with much accelerated approval by the US Food and Drug Administration and the European Medicines Agency in 2019. Cancer immunotherapy (sometimes called immuno-oncology) is to stimulate the immune system to treat cancer, to improve it. in the natural immune system. It is the use of basic research on cancer immunology and the growing subspeciality of oncology.

Cancer immunotherapy uses the fact that cancer cells often contain tumor antigens, the molecules on their surface can be detected by antibody proteins of the immune system, which bind to them. Tumor antigens are usually proteins or other macromolecules (e.g., carbohydrates). Normal antibodies bind to foreign viruses, but mutated antibodies bind to tumor antigens that mark and target cancer cells so that the immune system can block or kill. The clinical success of cancer immunotherapy varies greatly between different types of cancer; for example, some subfamilies of stomach cancer respond well to treatment while immunotherapy does not work in other subspecies.

KEYWORDS: *Biomarkers; Cancer; Immune checkpoint inhibitors; Immune-oncology; oncology*

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INTRODUCTION

Cancer incidence rates have steadily increased over the past 20 years, while mortality rates have shown a notable decline1. Although significant variations in survival rates are still observed among cancer types (i.e. there are more than 200 distinct diseases recognized), for most types, survival is improving thanks to early detection and improved treatments2,3. Treatment has undergone a slow evolution since its inception in the 1800s, with the sequential development of four major recognized treatment modalities. The first was surgery, made possible after the discovery of general anesthetics in the late 1800s4. This was a revolutionary development because it was the first time that the disease could be completely eradicated as long as the tumor was small and well defined. The second development was radiotherapy, born in the late 19th century, which uses X-rays and / or G-rays to damage the DNA within cancer cells, thus blocking essential biochemical processes and leading to cell death4. The third development, chemotherapy, was discovered in the 1940s, during World War II, when individuals exposed to mustard gas were observed to suffer from myelosuppression4. Doctors have speculated that patients with proliferative diseases (such as leukemia) might benefit from treatment with such agents that kill highly proliferating cells. Basically, the introduction of the first chemotherapy agents (analogues of nitrogen mustard gas) meant that tumors that were more complex or had metastasized and could not be successfully treated with surgery or radiation, could now be addressed. Additionally, chemotherapeutic agents have since been developed that act at different stages of the cell cycle and can be used in combination to prevent the development of resistance. The fourth development involved targeted

cancer therapies (also known as precision therapies). This was established with the discovery of imatinib (Glivec; Novartis) in the late 1990s, a small molecule kinase inhibitor targeting the mutant BCR-ABL protein found in cancer cells of patients with chronic myeloid leukemia (CML), but not in their health cells5. This concept of using modern structural biology and drug discovery methods to produce small molecules, proteins, antibodies and even cell therapies designed to target unique biomarkers associated with cancer cells, but not healthy cells, is now considered the approach. " gold standard "to discover new cancer treatments. Currently, four main treatment modalities - surgery, radiation, chemotherapy and targeted agents - are often used in combination to ensure that all cancer cells are eradicated from the body. Over the past decade, the first immuno-oncology (IO) treatments (e.g. checkpoint inhibitors) have emerged, which work by harnessing the body's immune system to kill cancer cells6. They are currently showing great promise in the clinic and are the main focus of this review. Immune checkpoint proteins are found on the surface of T lymphocytes and act as regulators of the immune system. They are essential for self-tolerance and prevent the immune system from indiscriminately attacking the body's cells, thus allowing a distinction to be made between "self" and "not-self" 7. Immune checkpoints also play a vital role in preventing uncontrolled immune responses by modulating the duration and magnitude of a physiological immune response, thereby preventing collateral damage, which is why the term "switch" is sometimes used to describe their role. Tumors are known to adopt certain immune checkpoint pathways as a mechanism to evade an immune response to them7. For example, some types of cancer cells express these proteins on their surface to disguise themselves, allowing them to go unnoticed by the immune system and promoting tumor progression8. PD-1 (programmed death 1) is an example of an inhibitory checkpoint receptor protein found on the surface of T lymphocytes that normally acts as an "off switch" after interacting with the PD-1 (PD-L1) ligand, a protein expressed on the surface of normal cells. However, PD-L1 is expressed by many types of cancer cells and up regulated in some, thus activating the 'switch' and protecting the malignant cells from an immune attack9,10. Immune checkpoint inhibitors (ICPi), such as anti-PD-1 / PD-L1 agents, prevent the interaction between PD-L1 on tumor cells and PD-1 on T cells, allowing the immune system to launch an antitumor response . Many observers believe that IO agents could become the fifth recognized cancer treatment modality in the next decade11,13. Some of the major ligands and receptors present on the surface of the tumor and immune cells that are targets for approved and emerging IO therapies are summarized in the following figure, Figure 1. [1][2]

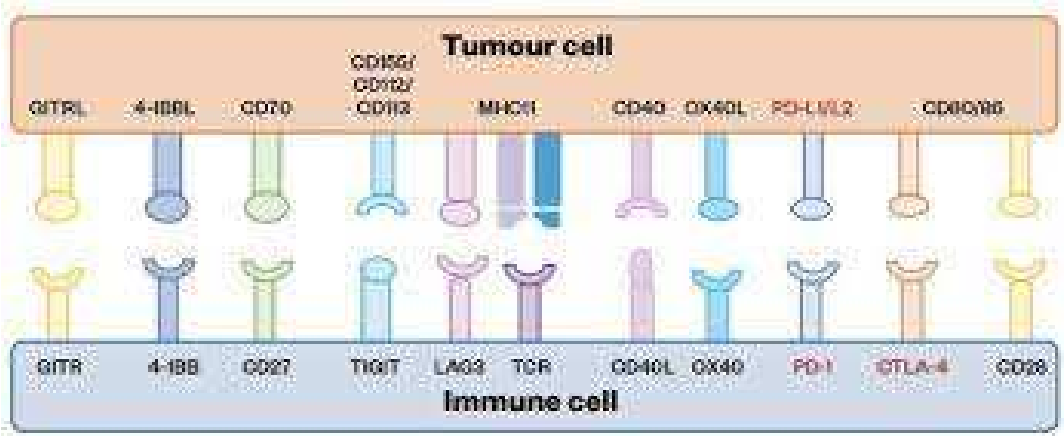

Figure-1: Some of the main ligands and receptors present on the surface of tumour and immune cells that are targets for approved and emerging immuno-oncology therapies

HISTORY:

It has long been known, but now increasingly, that tumor cells can be detected and disabled by the immune system. Some tumors show evidence of spontaneous degeneration at the beginning of their growth, suggesting that the immune system can detect and destroy early tumor cells.

Observation of spontaneous release in patients has led to the localization of IO. Spontaneous release is defined as a decrease in strength, or disappearance, of symptoms and signs of the disease, without any apparent cause and no treatment. This is often noted in patients who have recently had a serious illness, especially if this causes a fever that seems to trigger the immune system. It is now known that, in some cases, the immune system is able to completely eradicate the tumor. Spontaneous release has been observed in many types of cancer, but most commonly in advanced melanoma, renal cell carcinoma (RCC) and urothelial carcinomas, although this condition has been reported in breast cancer, neuroblastomas, other sarcomas and embryonal cancer.

William Coley was the first to investigate the power of the IO, and he successfully treated serious diseases based on the immune system in the 1890's. After discovering that cancer patients who contracted the disease after surgery appeared to be progressing faster than those who did not, she investigated the use of the virus to rejuvenate and improve the body's immune system to fight cancer. With these studies, he later developed Coley Toxin, which is based on reduced viruses and is thought to be the first known treatment for IO.

Recent developments include the Bacillus Calmette-Guerin (BCG) vaccine, which was introduced in the early 1900s to be used to fight tuberculosis (TB), and was first used to treat TB in the 1920s. However, its role in cancer treatment dates back to 1929 when a decrease in the incidence of cancer among TB patients was observed in autopsy. The experiments revealed that BCG produced a profound stimulation of the mononuclear phagocyte system (also known as the reticuloendothelial system), which was recognized as an important protection against cancer. In addition, it was noted that newborns vaccinated with BCG had significantly lower levels of leukemia later in life.

This background and basic understanding of IO aroused interest in the use of BCG in other types of fatal diseases, particularly bladder cancer. Preliminary studies have shown responses in patients with bladder melanoma when treated with intralesional BCG. As a result of this success, working on animal models has led to the publication of the results of the first successful clinical study of intravesical BCG in patients with recurrent bladder cancer.

It is now understood that intravesicular BCG binds to bladder tumors and urothelial cells using specific fibronectin and integrin receptors. Following exposure to macropinocytosis, the mononuclear phagocyte system is stimulated by BCG, creating a local inflammatory response characterized by the infiltration of granulocytes, macrophages and lymphocytes. Key elements of humoral immune reaction to BCG include interleukins (ILs) IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor alpha (TNF-a) and interferon gamma (INF-g). Recently, studies have shown that BCG contains high levels of CpG oligodeoxynucleotide motifs known to create TNF-related apoptosis-inducing ligand (TRAIL) through IFN production. Intravesical BCG has been shown to treat and prevent recurrence of some types of non-invasive bladder cancer.[3][4]

TYPES OF IMMUNOTHERAPY:

Several types of immunotherapy are used to treat the cancer given by the following.

- Immune checkpoint inhibitors, which are drugs that block antibodies. These test sites are a normal part of the immune system and keep the immune responses very weak. By inhibition, these drugs allow the body's cells to respond more strongly to cancer.
- T-cell transfer therapy, which is a treatment that enhances the natural ability of your T cells to fight cancer. During this treatment, immune cells are removed from your tumor. The ones that work best against your cancer are selected or modified in the lab to better attack your cancer cells, grow in larger clusters, and return them to your body with a needle in a vein. T cell transfer therapy may also be called cell therapy, adoptive immunotherapy, or immune cell therapy.
- Monoclonal antibodies, which are laboratory protein proteins designed to target specific cells in cancer cells. Some monoclonal antibodies mark cancer cells for better appearance and destroy the immune system. Such monoclonal antibodies are a form of immunotherapy. Monoclonal antibodies may also be called antibodies.
- Vaccines, which work against cancer by improving your immune system to cancer cells. Vaccines are different from those that help prevent infections.
- Immune modulators, which improve the body's response against cancer. Some of these agents affect specific parts of the immune system, while others affect the immune system in a normal way

Immuno-oncology is the study and development of therapies that help the immune system fight cancer.

Our immune system is a complex network of organs, cells, and molecules that protect us from foreign substances such as germs, fungi, and viruses. In addition to finding and destroying foreign substances, the immune system can detect and attack abnormal cells. [6]

There are two main components of the immune system:

- Congenital antibodies, innate immune system, immediate immune system and toxins.
- Flexible vulnerability is a learned defense system that grows as a result of exposure to an external object. Mutable antibodies work in two ways:

- Humoral, also called antibody-mediated, in which B-cells (a type of white blood cell called lymphocytes) produce antibodies (certain blood proteins) that target and destroy foreign substances.
- Cell-mediated, in which T-cells (another type of white blood cell or lymphocyte) identify and destroy abnormal cells, including cancerous ones.

Both the overactive and inactive immune system can be dangerous. Our growing understanding of the health benefits of a balanced immune system has led to the development of immunotherapies as a treatment for many types of cancer.

Current view on the anti-cancer response:

Challenges to improving the effectiveness of existing immunotherapies, as well as new developments, have led to a deeper understanding of the basic mechanisms of effective cancer-fighting immune responses, as well as "defects" that cause deficiency. an effective anti-cancer response in cancer patients.

The Cancer Immunity Cycle

Cancer immunization cycle, immunosuppression strategies and anti-cancer immunotherapy strategies. The cancer vaccination cycle (deepest circulation) begins when cancer cells release plant antigens. Antigen-presenting cells take up tumor antigens and deliver antigen-present peptides to immune cells, also activate the immune system to migrate during circulation, invade tumor sites, and kill cancer cells. The death of cancer cells triggers the release of additional tumor antigens, triggering an additional cancer vaccine. The immune system develops incorrect response loops to restore the anti-pathogen response. These negative feedback loops have been exploited by cancer cells to prevent cancer transmission (middle circle). Current immunotherapy cancers (external circles) have targeted and used a variety of methods in this cancer vaccine. There are two main approaches to cancer immunotherapy: a developmental approach, which aims to develop "normal" anti-cancer methods. Strategies at this stage range from the traditional indirect development of IL-2 signaling to the latest treatment of cancer-specific CAR-T cells; and conventional methods, aimed at reversing the negative effects of cancer on the surrounding plant environment. Strategies include FDA-approved immune checkpoint inhibitors and other developing drugs (e.g., adenosine pathway inhibitors). [7]

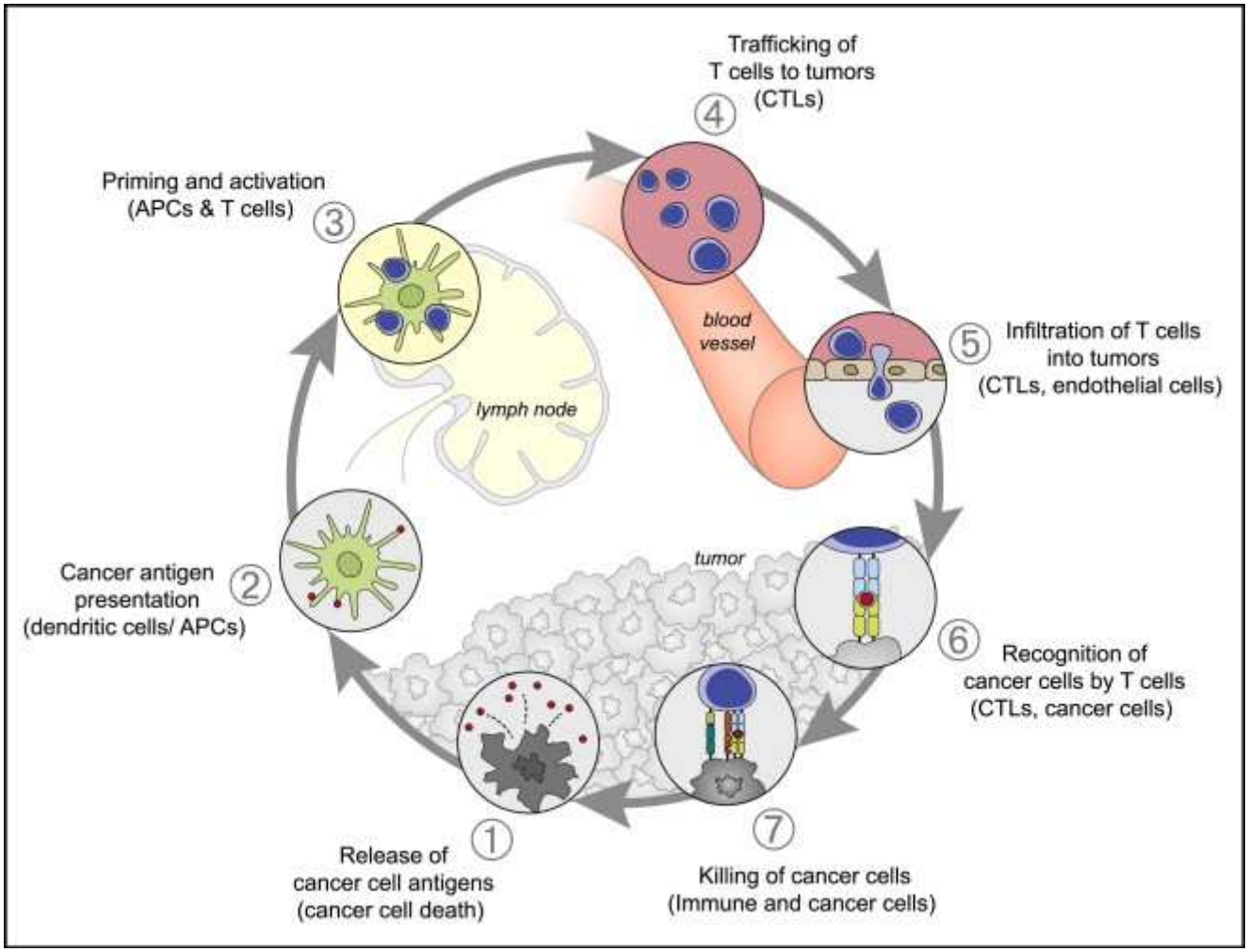

Figure-2: Cancer immunity cycle

Once activated, active T cells enter the body systematically, invade the cancer site, detect cancer cells that produce peptides derived from tumor antigen introduced by the Major Histocompatibility Complex (MHC), and kill targeted cancer cells. Next, cancer cells that release neoantigen (s) are introduced in contrast to APCs, leading to an increase in the immune response to cancer by allowing the activation and activation of other T cells to detect and attack the tumor. As with any immune response, the final phase of the cancer-fighting response is governed by a complex network of stimulant and inhibitory pathways. The PD-1 / PD-L1 method is one of the main blocking methods. The involvement of TCR with the cognate antigen-MHC complex, as well as cytokine stimulation (e.g., IL-2 stimulation), triggers the expression of PD-1. The integration of PD-1 and PD-L1 into target cells inhibits T-cell proliferation and IL-2 production, reducing immune response. Therefore, rational integration of immunotherapy should be aimed at facilitating the integration of T cell function and effector function, as well as systematic suppression of T cell inhibitory processes. [8]

Mechanism of Action

Antibody-dependent cell-mediated cytotoxicity (ADCC)

Antibody-dependent cell-mediated cytotoxicity (ADCC) based on the human body requires antibodies to bind directly to the cell surface. Antibodies are made up of the binding site (Fab) and the Fc region that can be detected by immune cells through their Fc surface receptors. Fc receptors are found in many immune cells, including NK cells. When NK cells meet with antibody-associated cells, the latest Fc regions interact with Fc receptors, releasing perforin and granzyme B to kill the tumor cell. Examples include Rituximab, Ofatumumab, Elotuzumab, and Alemtuzumab. Developmental antibodies alter Fc regions with high affinity for a specific type of Fc receptor, FcγRIIIA, which can significantly increase efficiency.

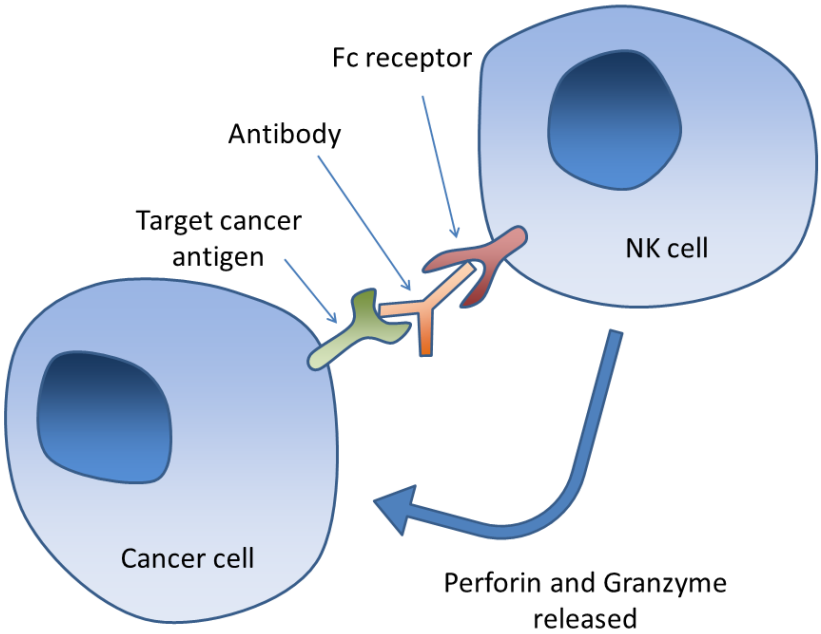

Figure-3: Antibody-dependent cell-mediated cytotoxicity.

When Fc receptors in natural killer cells (NK) interact with Fc regions of the immune system bound to the cancer cells, the NK cell releases perforin and granzyme, leading to apoptosis of the cancer cell.

Complement Activation

The synthesis system incorporates blood proteins that can cause cell death after the antibody binds to the cell site (the old filling method, among the accompanying opening methods). The system usually works with foreign viruses, but can be activated by the immune system to treat cancer. The process can be started if the antibody is chimeric, human or human; as long as it contains the IgG1 Fc region. Coherence can lead to cell death by activating the membrane attack complex, known as filler-dependent cytotoxicity; development of cytotoxicity-dependent antibody cells; and cell-based cytotoxicity of CR3. Complete-dependent cytotoxicity occurs when the immune system binds to a cancer cell, the C1 complex binds to these antibodies and later forms protein molecules in the cell membrane.

Blocking

Antiretroviral drugs can also be effective in binding proteins and preventing them from interacting with other proteins. Checkpoint inhibitors (CTLA-4, PD-1, and PD-L1) work in this way. In short, protein checkpoint inhibitors often help to reduce the immune response and prevent the immune system from invading normal cells.

Checkpoint inhibitors bind these proteins and prevent them from functioning normally, which increases the body's immune system.

Eg. They include durvalumab, ipilimumab, nivolumab, and pembrolizumab.

Immuno-Oncology

The field of Immuno-Oncology (O-O) was transformed with the discovery of T-cell immune system test sites CTLA-4 and PD-1. Preventing this has led to a number of autoimmune events, but also improved immune responses. These results confirmed that abscesses suppress the immune system as a means of ensuring their survival, and led to the idea that the immune system could be integrated to control many cancers affecting a wide variety of cells and tissues.

Ongoing clinical trials test the strength of other antibodies as researchers seek ways to overcome toxicity for antibodies. Some active areas of IO research are looking for new ways to identify tumors by understanding their surrounding environment, which includes investigating the potential of 'metabolic test sites', and understanding the impact of a patient's microbiome in response to immunotherapy.

The immune system is now known to detect and respond to abscesses through a process known as immunosurveillance. Immune systems using the recognition of viral or mutated proteins are expressed in the tumor site - tumor antigens - to do this. However, plants have their own immune systems that make these immune responses ineffective.

IO therapies, from monoclonal antibodies to cellular vaccines, stimulate or inhibit antibodies to increase a patient's response to a tumor. This approach is different from 'targeted' remedies, directing the tumor directly or aiming to disrupt the blood supply of the tumor, as well as traditional chemo- and radiation treatment that causes 'collateral' damage to healthy cells.[9][10]

I-O therapies are the next generation of cancer treatment

In responding patients, IO treatment can provide longer clinical outcomes than traditional therapies such as chemotherapy and radiotherapy and, in some cases, contribute to complete tumor regression. IO therapies also have a small negative impact on the quality of life of patients due to the low incidence of severe adverse events.

However, not all patients respond to I-O treatment. There is the issue of tumor heterogeneity; the cancer cells inside the tumor change over time into smaller amounts with varying degrees of sensitivity to cancer treatment. There are also many naturally occurring mechanisms available to prevent autoimmunity in the human body, which can reduce the effectiveness of these therapies. GSK developed cancer immunotherapies designed to identify these control mechanisms as a means of improving response rates in cancer patients.

Overview of the cancer immunoediting model

In 1908, Paul Ehrlich predicted that cancer would be "extremely rare" if it were not for the immune response that inhibited the growth of advanced cancer cells. At the time, it was difficult to test this hypothesis by testing as there was limited understanding of the immune system, and suitable models such as inbred transgenic mice were not yet available. In the late 1950's, studies showing the existence of tumor-related antigens led Burnet and Thomas to build on Ehrlich's observations, thereby promoting the concept of cancer prevention. The theory is that cellular defense mechanisms can detect the different antigens produced by cancer cells and eradicate them before they come to the clinic as tumors. These tumor antigens can be viral proteins found in viral tumors, neo-antigens from mutated proteins or highly self-expressed antigens.

The concept of cancer prevention was demonstrated in several studies using genetically modified mice that did not have antibodies such as T and B cells. For example, it has been shown that mice deficient in natural active cells (NK) T, γδ T cells, NK cells, αβ T cells, interferon (IFN) -γ or interleukin (IL) -12 showed an increase of tumors in comparison. in wild-type mice. Similarly, in clinical studies, transplant patients and people with a variety of antibodies show a highly correlated risk of cancer progression.

Recently, the cancer immunosurveillance hypothesis has shifted to the "cancer immunoediting" model, which provides more details on the interaction between the immune system and cancer. In contrast to the immunosurveillance hypothesis, the immunoediting model emphasizes the body's ability to not only destroy immunogenic cancer cells, but also to produce a variety of reduced cancer cells that stimulate the anti-tumor immune response. Cancer immunoediting is also defined as a process driven by the immune system of tumor antigens, leading to tumor loss (phase elimination), immunosuppression control of the remaining cancer cells (stage stage), or evasion of immune control through tumor (escape phase) . Below we describe these three Ess of cancer immunoediting.[11][12][13][14]

Cancer immunoediting progresses in three stages:

Completion, equality and escape. Cancer immunoediting tests occur during tumor growth but also in patients receiving anticancer immunotherapies. Congenital resistance and the benefit of immunotherapy are important barriers to effective treatment.[15]

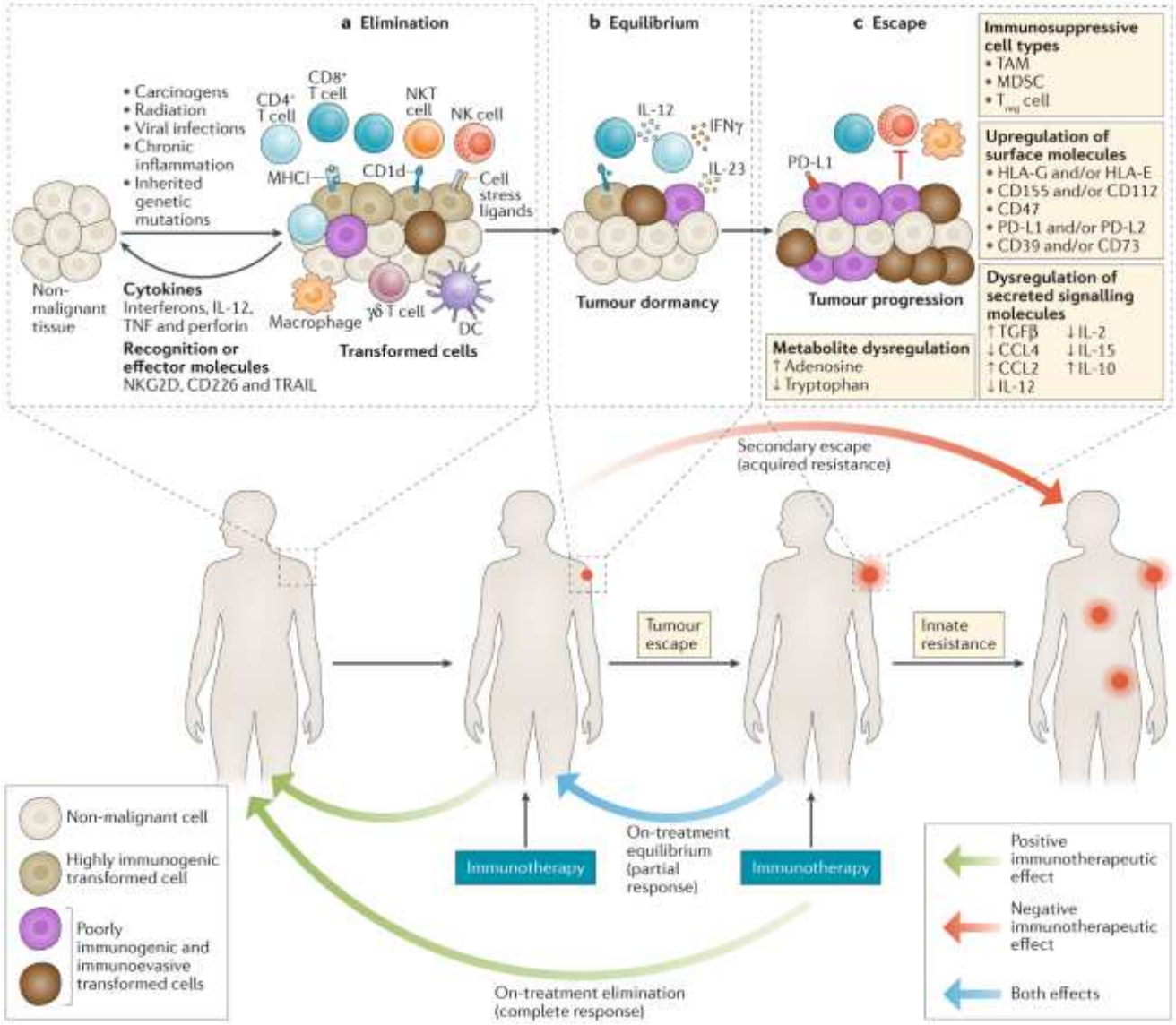

Figure-4: Cancer immunoediting

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