Review

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Unraveling the Complexity of Immune System & Tumor Cells; A Narrative Overview

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Review

Unraveling the Complexity of Immune System & Tumor Cells; A Narrative Overview

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Abstract

Introduction- Undergoing drastic metabolic and behavioral transformations, carcinogenesis is a cumulative process which leads to excessive proliferation in an unusual manner, camouflage to escape surveillance by the immune system. Aim-The aim of this review is to provide an in-depth exploration of immunology of cancer, highlighting the mechanisms and various aspects immune system, how it interacts with cancer cells and the challenges coming in its way due to tumor cell immune evasion. Method-A comprehensive literature survey and search was made across major electronic databases, which include PubMed, Scopus, and Web of Science, covering publications up to June 2025. The search strategy employed combinations of keywords and medical terms relevant to tumors. Conclusion-Representing one of the most significant advances in the field of oncology the evolving field of cancer immunotherapy offers promising treatment options thereby harnessing the body's immune system to target cancer cells. Justification-it is not our intention to revisit many of the issues relating to tumor immunology, which have already been covered in detail previously in the literature. Rather this article focuses on the aspects that by compiling desperate foundational knowledge and parallel newer advances in this rapidly evolving field, the review offers a holistic framework of worth to our researchers, clinicians, and students working in the area of cancer immunology and oncology.

Keywords: cancer immunotherapy; CAR-T cell therapy; immune checkpoints; immune evasion; tumor microenvironment; TCLs; Immune tolerance

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1. Introduction

The cancer-immunology refers to a cycle which states a series of events involved as anti-cancer immune responses. Describing the comprehensive approach, cancer immunity involves varied events including killing of tumor cells by T cells, antigen presentation & T cell stimulation in the lymph nodes, trafficking and infiltration of these tumor cells inside of tumor mass and their recognition, generation of antigen specific tailor made effector and memory T cells stimulation of humoral immune system maintaining active immunity. All these events including effector T cells and other residing immune cells & tumor antigen specific antibodies work cumulatively eliminating cancer leading to final adaptation to tumor evolution [1]. Any deviation in any of this sequence of events can become rate-limiting, checks the capability of immune system to control tumor growth. All this favours the cumulative process in which tumor cells undergo intense metabolic and behavioral changes [1,2], resulting to excessive proliferation in an untimely way. Understanding the mechanism of checkpoint inhibition [3], tumor microenvironment [3,4], role of dendritic cells as anticancer tool has given a new insight to the view closely the complexity of cycle and also provides new targets for research and therapeutic intervention. Tumors have evolved sophisticated mechanisms to evade immune detection through various means. These include the loss of tumor

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antigen expression, which prevents recognition, the recruitment of immunosuppressive cells, and the upregulation of immune checkpoints. Collectively, these tumor escape strategies facilitate the uncontrolled growth and progression of cancer tissues, as well as further metastasis. Emergence of immunotherapy proved to be promising tool harnessing the immune system to fight cancer. Discovery of adoptive cell therapies involving infusion of tumor specific T cells and Natural Killar cells in patients, Immune check point inhibitors to block inhibitory receptors, monoclonal antibodies and cancer vaccines are some of the major key strategies which have potential to effectively target cancer cells and enhance the immune response. Despite their effective role to check cancer development still many challenges persist just like tumor heterogeneity, treatment resistance and other immune related adverse responses [3,4].

2. Historical Perspective

Our ancient knowledge of wisdom about immunity was engraved in scriptures of Ayurveda. According to Acharya Charaka quote, oja (immunity) appeared first in the human body during embryogenesis [5] and the body consist of seven dhatus (seven bodily tissues as from Rasa to Shukra Dhatu), called saptdhatus. The essence of these saptadhatus which are Rasa (plasma and lymph), Rakta (blood cells), Mansa (connective and muscular tissue), Meda (body fats, such as adipose tissue), Asthi (bones), Majja (bone marrow), and Shukra (reproductive systems) collectively constitute Oja. Oja is considered the foundation of strength, hence it is referred to as Bala, which denotes the capacity to resist external threats5, 6. A reduction in Ojas, termed Ojakshaya, is primarily attributed to factors such as anger, hunger, worry, grief, and exertion [6,7]. This diminution results in symptoms such as irritability, debilitation, unwarranted anxiety, discomfort in sensory organs, poor complexion, impaired speech, and skin dryness. All these events make a person disease prone [7,8].

Modern medicine had concept of immune system as innate /acquired or adaptive. Active immunity or passive immunity gained by various means, but both old and new concepts have common theory of birth or innate system of immunity, and both systems also believes in acquiring immunity from outside after birth [9]. Cancer was also termed as "Arburd" according to ancient system of medicine and it was compared to a demon itself engulfing all tissue coming in its way [10]. Fight against cancer is not new but age-old continuous process and scientist and doctors all over the world are trying to overcome but it becomes a new puzzle every day.

3. Modes of Carcinogenesis

Cancer is characterized by its unpredictable manifestation, progression, and outcome in each individual, with variations occurring at both the cellular and molecular levels. Carcinogenesis is a cumulative process wherein cells undergo significant metabolic and behavioral alterations [11], leading to excessive and untimely proliferation, thereby evading immune system surveillance12. This process culminates in the invasion of distant tissues to form metastases, facilitated by the accumulation of genetic modifications that regulate cellular activities such as proliferation, lifespan, reproduction, and immune evasion [12,13]. The formation of a mass of deregulated cells that do not adhere to the norms of regular cell growth and behavior results in carcinoma. Such a mass often remains asymptomatic for an extended period. However, it eventually disrupts normal physiological functions, leading to a range of symptoms that vary depending on the mass's location, size, and the extent of cancer cell dissemination within the organism.

4. Cancer Genes [14]

According to available literature, human DNA comprises approximately 23,000 genes, with about 3,000 to 5,000 of these coding for proteins that play roles in genetic sequences and are deregulated in cancer [15]. When a gene malfunctions, it can result in the production of abnormal amounts of a vital protein (either excessive or insufficient), the creation of an atypical protein (with either enhanced or diminished function), or the complete lack of the

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Protein.

Box 1: Mutation in **Kirsten rat sarcoma (KRAS) gene [14]** leads a small protein inside the cell membrane to an amplifier of cell growth signalling. This protein works as a signal between receptors for growth factors at the cell surface and the genetic wiring systems that send growth signals to the cell nucleus to endorse cell division and on being mutated this protein behaves like a switch which is locked in the "on" position breeding a permanent cell division signal. Mutations of KRAS are common in many cancers, such as colorectal cancers or adenocarcinomas of the lung. This type of activated gene is called an "oncogene".

Box 2: Tumor protein 53 (TP53) [14,15]
Inactivation of some genes contribute to cancer development like TP53gene. TP53 gene encodes a protein that is an "emergency brake" of cell to avoid untimely cell division and mutation in this gene disrupts the protein, which switches on the unwanted proliferation of cells Mutations in TP53 has been observed in nearly all types of cancer. The type of genes that contributes to cancer development by loss of its function are called a tumour suppressor, as in normal cells its active products work as a brake to suppress cancer growth.

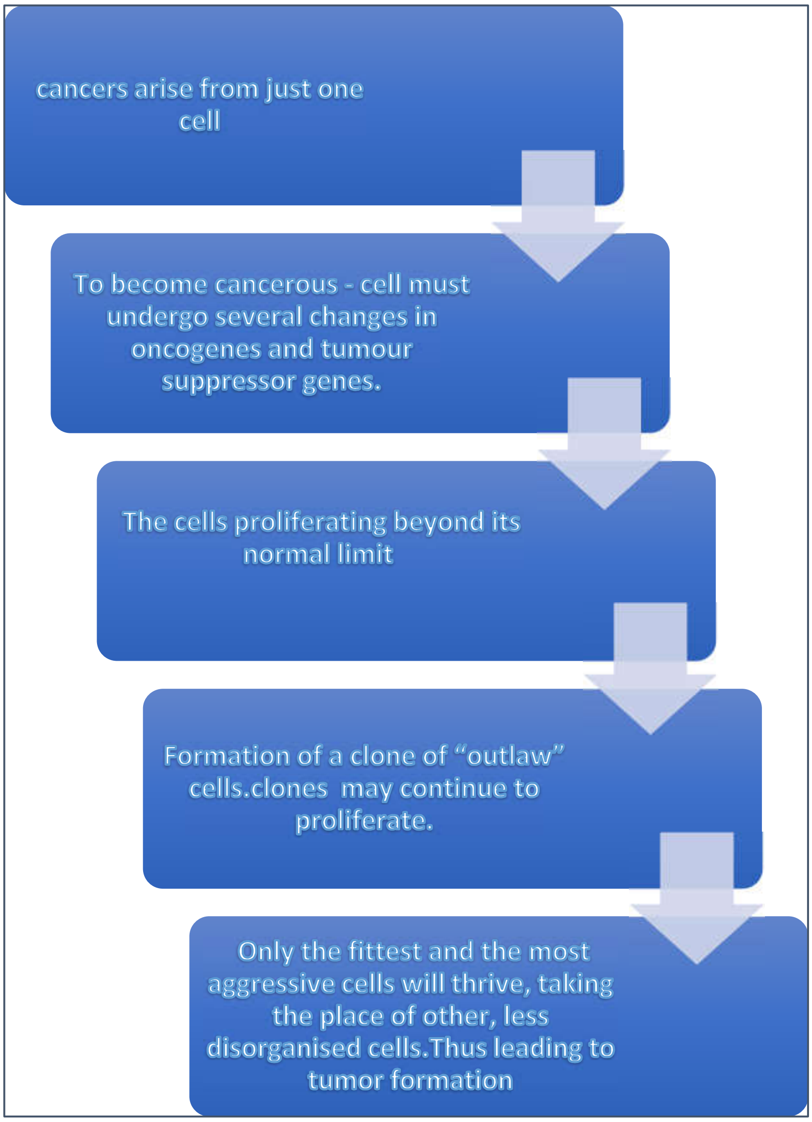

Figure 1. CASCADE OF CANCER [16].

5. Riots in the Genetic System

Cancer originates from minor alterations in DNA sequences, referred to as mutations [17]. These mutations may involve a single base change, resulting in the incorporation of a different amino acid into a protein, thereby altering its function. Additionally, DNA alterations can occur across a large number of bases through translocation or fusion of gene segments, leading to the synthesis of novel, abnormal proteins [15–19]. Importantly, these genetic mutations or alterations can be identified by sequencing the DNA of cancer cells [19].

6. Modification in the DNA Packaging /Epigenetic Changes-

DNA is organized into two primary regions: (a) "closed" regions, which are not accessible for editing or replication, and (b) "open" regions, which can be transcribed, read, and utilized by the cell for the synthesis of RNA and proteins [15]. The processes of DNA transcription and replication are heavily influenced by the manner in which DNA is compacted, packaged, and organized. Modifications in this organizational system can lead to the repression of genes in open regions or the activation of genes in closed regions [15]. To identify these changes, it is essential to examine the chemical modifications that control the accessibility and readability of DNA.

These alterations cannot be detected just by sequencing DNA. Such changes are called "epigenetic" [15] and only recently the role of epigenetic changes has been recognised. Genetic or epigenetic changes influence and respond to each other, thereby sequential changes happen via newly generated paths that decide upon how a given cell will progressively acquire the characteristics of a cancer cell [15,17]. Both the genetic and epigenetic alterations are universally present in human cancer which can be transmitted to their daughter cells over many cell generations. [15,18]. The causes of changes are many. The genome comprises 3 billion base pairs, each of which can undergo modification through interaction with various chemical, physical, or toxicological agents [20]. Disruptions in epigenetic states may also lead to functional consequences analogous to those caused by genetic alterations [15].

BOX3: Carcinogens interact with DNA bases, binding to them and inducing specific modifications within the coding sequence. Ultraviolet (UV) light can cause the formation of dipyrimidine dimers by linking adjacent cytosines, resulting in double mutations where two cytosines are replaced by two thymines. These mutations serve as a "signature" of UV light-induced mutagenesis in skin cancers [21]. Ionizing radiation may lead to single or double DNA strand breaks [22].

7. Error of DNA Replication and Repair-

The primary cause of DNA damage is attributed to errors in the DNA replication and repair systems [15]. Each cell division necessitates an impeccably accurate replication of the 3 billion base pairs of DNA [20], a process that is meticulously monitored and regulated through DNA proofreading and repair mechanisms. Nevertheless, errors may occur and, if left undetected or uncorrected [15], could prove detrimental. Such disruptions may endow cells with novel properties, potentially contributing to the chaotic environment characteristic of a proliferating cancerous mass [15–17]. Consequently, the cell may adapt to these conditions and progress to form part of a malignant tumor [15].

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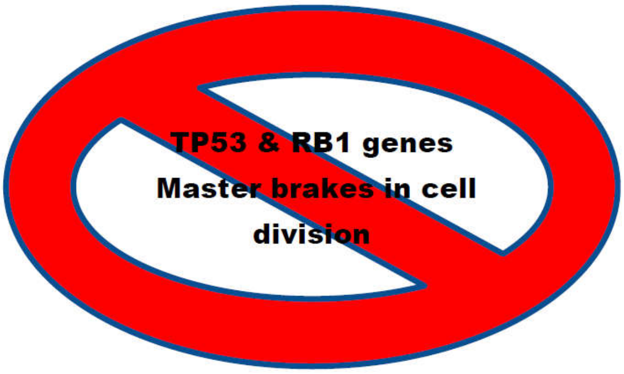

Figure 2. TP53 &RB 1 GENES [16].

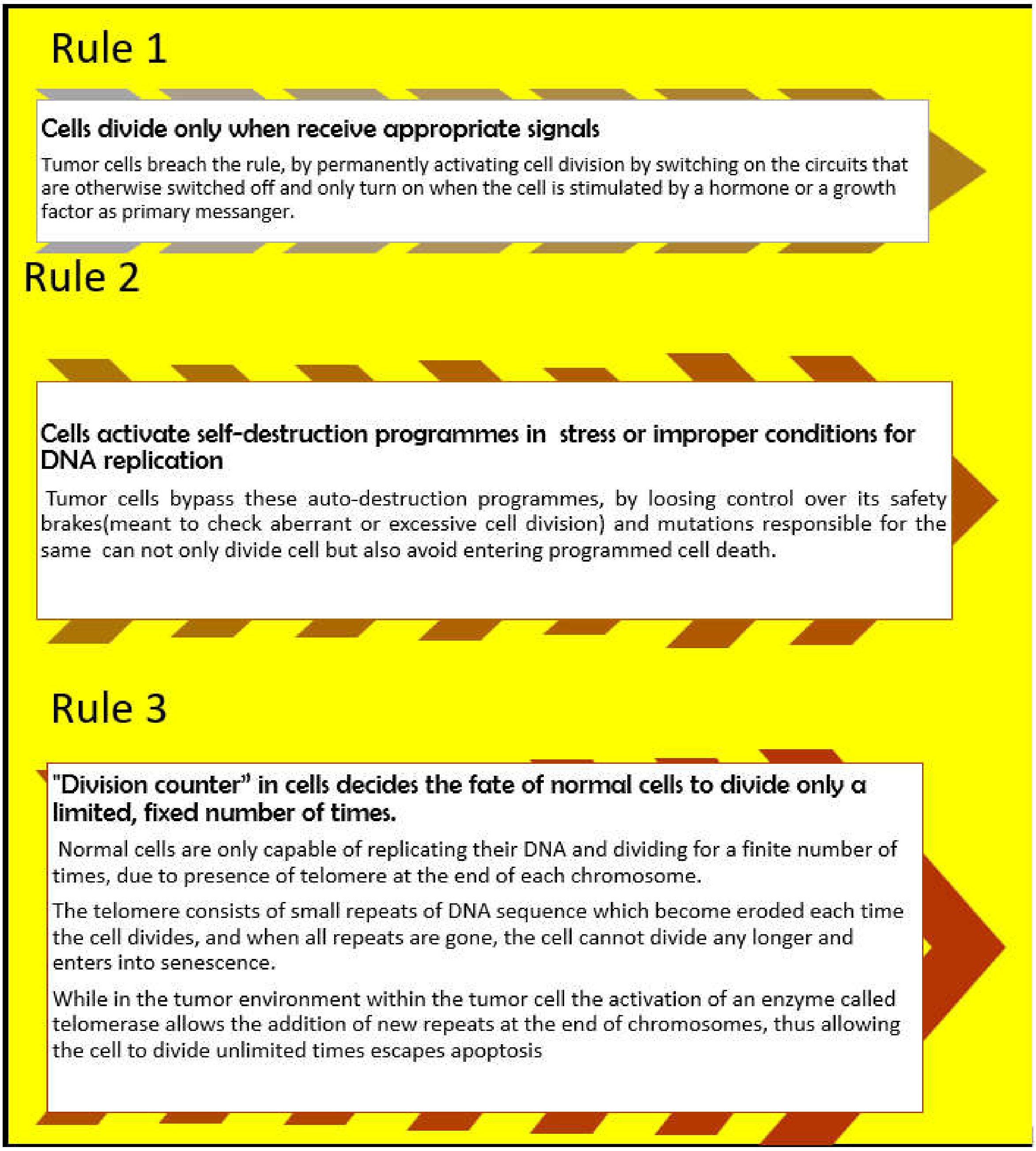

Figure 3. Cancer violates rules [16].

Table 1. ONCOGENES AND TUMOR SUPPRESSOR GENE [23].

ONCOGENES	TUMOR SUPPRESSOR GENES
PDGF- glioma (a brain cancer)	APC: colon and stomach cancers
EGFR –glioblastoma and breast cancer	DPC4; pancreatic cancer
HER-2 or ERBB2- breast, salivary gland and ovarian cancers	NF-1: neurofibroma and pheochromocytoma (cancers of the peripheral nervous system) and myeloid leukemia
RET- thyroid cancer	NF-2: meningioma and ependymoma (brain cancers
KRAS- lung, ovarian, colon and pancreatic cancers	CDKN2A or MTS1: wide range of cancers
NRAS- leukaemia	RB1: retinoblastoma and bone, bladder, small cell lung and breast cancer
MYC1- neuroblastoma	TP53: wide range of cancers
NMYC-(a nerve cell cancer) and glioblastoma	WT1: Wilms' tumour of the kidney
LMYC- lung cancer	BRCA1: breast and ovarian cancers
BCL2- B cell lymphoma	BRCA2: Involved in breast cancer
CTNB1-liver cancer	VHL: renal cell cancer
MDM2- sarcomas (connective tissue cancers)	
PDGF: platelet-derived growth factor. **EGFR: receptor for epidermal growth factor.** **HER-2 or ERBB2: human epidermal growth factor receptor.** **RET: growth factor receptor.** **KRAS: Kirsten RAt Sarcoma virus.** **NRAS: Neuroblastoma RAS viral oncogene.** **MYC1, NMYC, LMYC: Myc family members.** **BCL2: B-cell lymphoma 2.** **CCND1: B-cell leukemia/lymphoma 1 or PRAD1: parathyroid adenomatosis.** **CTNB1:** beta-catenin. MDM2: murine double minute 2	**VHL: Von Hippel–Lindau,** **BRCA2: breast cancer type 2,** **BRCA1: breast cancer type1,** **CDKN2A or MTS1: cyclin-dependent kinase Inhibitor 2A,** **NF-2: neurofibromatosis type2** **NF1: neurofibromatosis type 1,** **DPC4: Deleted in Pancreatic Cancer, locus 4,** **APC: Adenomatous polyposis coli**

8. Primer of Immunity

Cancer cells are aberrant cells that deviate from the regulatory mechanisms governing normal cellular life, thereby achieving autonomous survival. In this process, cancer cells endeavor to adapt and evade the host organism's defense systems, progressively becoming more aggressive and invasive [20]. They possess the capability to disseminate throughout the body, preferentially colonizing conducive environments as metastases [20,24]. Despite many brilliant discoveries around the world, cancer continues to flee cures and, as a result its image is always changing. After reviewing so many cancer researches, Hanahan and Weinberg proposed six hallmarks representing cancer cell are [18]: capacity to sustain proliferative signalling, to resist cell death, to induce angiogenesis, to enable replicative immortality, to activate invasion / metastasis and to avoid growth suppressors [18]. In 2011, four additional hallmarks were proposed, with two of them emphasizing the newly recognized dual interaction between cancer and the immune system. These hallmarks include the ability to evade immune destruction, leading to acute inflammation and subsequent cancer elimination [18,25], as well as the potential for chronic inflammation, which instead supports tumor growth rather than its elimination [18,25].

This review lays its focus on discussing various relations involved in immune system with cancers. Immunology, has provided important direction in cancer understanding and as a result, immune-based therapy are in main focus of drug companies for developing anticancer treatments. The elementary role of our immune system is to protect human beings against foreign invaders (bacterial/viral), the responses consist of two types, humoral immunity [23] and cellular immunity [26], which mediate the immune response through B and T lymphocytes as well as their products. Humoral immunity [27] can neutralize and eradicate outside pathogens via B cell antibodies through the phenomenon of opsonization. Whereas cellular immunity responds more quickly by working through recognition of antigens, activation of antigen presenting cells (APCs), activation and proliferation of T cells [26,27]

9. Innate Immunity

Injuries (genetic or epigenetic) to normal healthy cells stimulates front-line defense mechanism, the innate immune system, which reacts against injury immediately [28]. These cells could become target of malignant conversion and reflect additional characteristics, allowing their uncontrolled proliferation, survival, and dissemination [28,29]. The natural killer (NK) cells possess the ability to distinguish between normal and tumor cells through a complex process involving the expression of various inhibitory and stimulatory molecules [30]. A variety of receptors, known as natural cytotoxicity receptors (NCR), are expressed on the surface of NK cells. These include molecules such as NKp46, NKp30, NKp44, and NKG2D31, which bind to specific ligands of the Major Histocompatibility Complex (MHC) class I. The interaction between MHC-I related ligands and NKG2D initiates the activation of NK cells, NKT and $\gamma\delta$ T cells [32], as well as cluster of differentiation (CD) 8 T cells. These activated cells inhibit tumor cytotoxicity and the production of interferon (IFN)-γ. The extracellular release of cytoplasmic stress molecules, such as uric acid, activates macrophages and dendritic cells (DC), leading to the production of interleukin (IL)-12 and a shift towards adaptive immunity [31,33].

10. Role of NK Cells

NK cells have been able to have antitumor activity by chemokines, cytokines and growth factors production [34]. They destroy cancer cells via direct mechanisms of - secretion of tumour necrosis factor (TNF)-α [35], perforin [36], cytoplasmic granules [37] and granzymes [38], expression of death receptor-mediated apoptosis [39], and expression of CD16 [40] which leads to antibody dependent cellular cytotoxicity (ADCC).

11. Role of Macrophages

Macrophages are vital module of tumors stroma and tumor-associated immune dysfunction, which are known as pro-inflammatory M1 or anti-inflammatory M2 macrophages [41]. M1 macrophages work by secreting pro-inflammatory cytokines to boost antitumor immunity, whereas M2 macrophages secrete anti-inflammatory cytokines to promote tumorigenesis [41]. Myeloid-derived suppressor cells (MDSCs) are immature and immunosuppressive cells are raised in inflammatory diseases, especially tumors [41,42]. Many inhibitory factors such as IL-10 and arginase are secreted by these cells in order to inhibit T cells and promote Regulatory T cells (Tregs) and detrimental M2 macrophages, overall suppressing anti-tumor immunity [43].

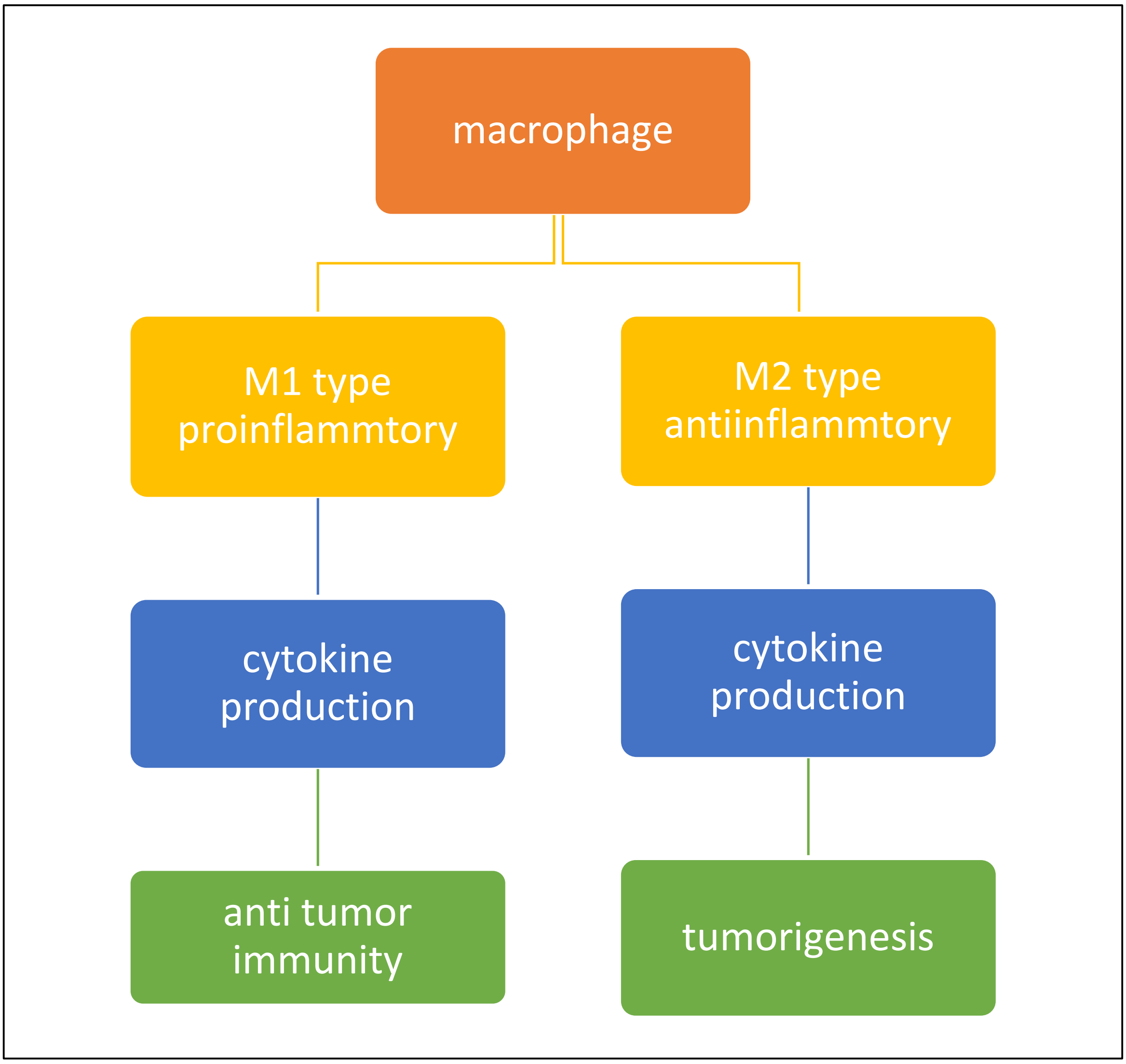

Figure 4. MACROPHAGE SYSTEM [41].

12. Adaptive Immunity

The adaptive immune response, often referred to as the "second-line" response, is initiated subsequent to the rapid onset of the innate immune reaction. This response is activated by dendritic cells (DCs), which capture, process, and present tumor antigens to major histocompatibility complex (MHC) class I and II molecules. This process stimulates antigen-specific T- and B-lymphocytes, thereby initiating the cellular response, followed by the specific production of antibodies, constituting the humoral component [44,45]. Macrophages, DCs, and antigen-presenting cells (APCs) are the primary entities that recognize foreign cells and engage in the immune response against potentially harmful invaders [46]. They eliminate target invaders (antigens) through phagocytosis or receptor-mediated endocytosis [44]. These cells fragment and process proteins into peptide sequences, which are then presented on the extracellular membrane surface of APCs within the context of MHC class II [44,47]. Additionally, these cells produce a substantial amount of various cytokines, thereby promoting the immune response. In this manner, APCs function as a bridge between the innate and adaptive immune systems by recognizing foreign antigens and presenting them to naive T cells [48].

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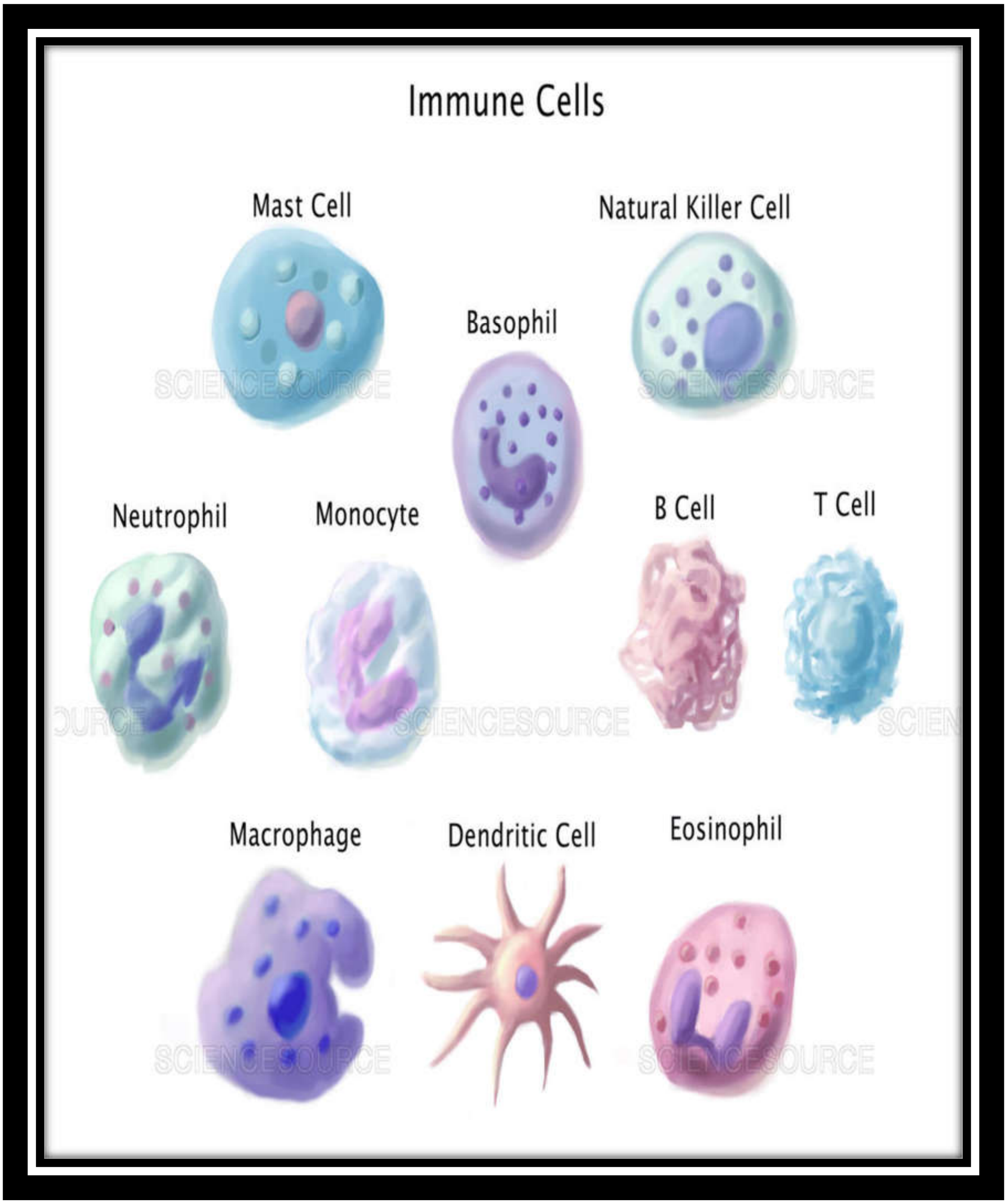

Figure 5. Immunity producing cells [49].

13. Cascade of Immune Response

Once the immune response is triggered,

- ✓ The foreign antigen is presented to specialized cells of the immune complex.
- ✓ B-lymphocytes are formed and differentiated in the bone marrow and enter into the blood stream as functionally viable cells.
- ✓ These B cells have a receptor on their surface that binds to a specific antigen. Upon encountering this antigen, the B cells begin to divide and eventually transform into plasma cells, which then release antibodies—soluble immunoglobulin molecules—into the bloodstream.
- ✓ T cells are produced in the bone marrow and migrate to the thymus for process of maturation.
- ✓ Immuno-competent T cells leave the thymus and enter into the circulation.
- ✓ On encountering target, T cells kill by induction of apoptosis in the infected or cancerous cell.

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- ✓ Tumor-infiltrating lymphocytes (TILs) have abundance of cytotoxic T lymphocytes (CTLs) which are capable of invading cancer cells
- ✓ Mode of attack of CTLs on tumor cells is via perforin, granzymes and also ligands of the TNF superfamily.
- ✓ Few lymphocytes become sensitized for life long as memory cells, recognizing only a single antigen, posed to respond for future encounters.
- ✓ The regulatory T cells (T-regs) represent a distinct subset of T cells characterized by the expression of the CD25 glycoprotein. These cells play a crucial role in the recognition of self-antigens, thereby preventing the onset of autoimmune responses.

Box4: Different T cells are classified on the basis of function and phenotype. T helpers are the largest of all T cells expresses CD 4 glycoprotein. By secreting cytokines they enhance the immune response and direct cell-to-cell contact. Other specific functional CTLs, express CD8 glycoprotein and can directly kill the antigen-containing cells [50] (virally infected or cancerous).

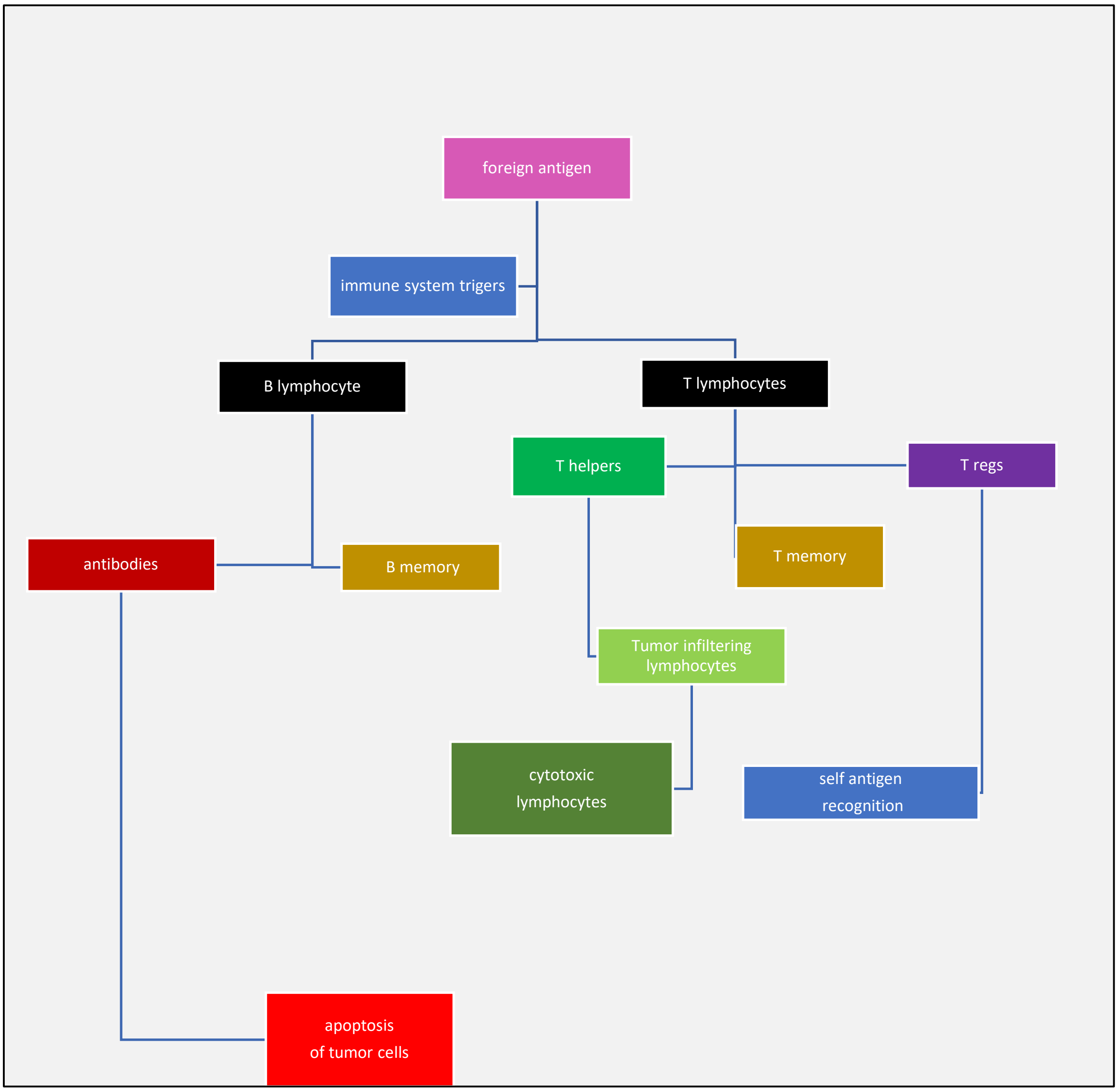

Figure 6. IMMUNE SYSTEM AGAINST TUMORS [50].

14. Human Tumor Associated Antigens

Identification of Tumor Antigens. Antitumor cytotoxic T lymphocyte (CTL) clones have been isolated from the blood or tumors of patients. The term "expression cloning" is employed to identify the peptides recognized by such CTLs. This method involves isolating the peptide-encoding gene by transfecting a library of tumoral cDNA and testing the transfected cells for their ability to activate the CTL clone [51,52]. Fragments of the identified gene can then be transfected to define the region encoding the antigenic peptide. Subsequently, candidate peptides with appropriate human leukocyte antigen (HLA)-binding motifs are tested for their ability to sensitize tumor cells to lysis by the CTL [51]. Another method, "reverse immunology," is often used to identify tumor-associated antigenic peptides. This approach involves selecting peptides with suitable HLA binding motifs within a protein of interest, such as proteins encoded by mutated oncogenes or genes selectively expressed or overexpressed by tumors. Another identification method is based on the "elution of antigenic peptides" from MHC class I molecules that are immune-purified from the surface of tumor cells [52,53].

High Tumor Specificity Antigen. Antigens derived from viral proteins [54], point mutations [55], and encoded by cancer-germline genes [56] are three classes of antigen which can induce tumor-specific T cell responses as they manifest a tumor-specific pattern of expression.

Viral Antigens. Viruses cause of several types of cancers such as cervical, nasopharyngeal, hepatic, leukemias. Viral proteins are produced inside the tumor cells and so antigenic peptides can be detected by T cells [54].

Antigens Encoded by Mutated Genes. Numerous cytotoxic T lymphocytes (CTL) derived from cancer patients have demonstrated the ability to recognize antigens generated by point mutations or frame shifts, which result in the production of novel antigenic peptides. In contrast, only a limited number of CD8 T cells recognize peptides derived from genes frequently mutated in cancer, such as P53, KRAS, or NRAS [55,57]. An additional significant source of tumor-specific antigens is the cancer-germline genes, which include the melanoma-antigen encoding (MAGE) genes. These comprise 25 functional genes clustered in three regions of the X chromosome, namely MAGE A, MAGE B, and MAGE C. Cancer-germline genes are expressed in a wide variety of cancers but are not present in healthy tissues, with the exception of germline and trophoblastic cells [56,58].

Antigens with Low Tumor Specificity. Antigens can be categorized into differentiation antigens and those derived from genes that are overexpressed in tumors. Differentiation antigens originate from proteins expressed in both tumor and corresponding healthy tissues [59]. Notably, differentiation antigens have been identified in melanoma cells, where the associated proteins are involved in melanin biosynthesis or melanosome biogenesis [60]. Additionally, peptides have been identified from the prostate-specific antigen [61] and prostatic acidic phosphatase [62], which are expressed in both normal [63] and tumor prostate tissues [64]. Carcinoembryonic antigen (CEA) is expressed in colorectal cancer and various other epithelial tumors, and it is also present at lower levels in a range of normal epithelial cells within the intestinal tract [65,66].

Overexpressed antigens hold significant potential for the development of immunotherapeutic vaccines [67]. However, accurately quantifying their expression levels on the surfaces of tumoral versus normal cells presents a substantial challenge. This quantification is crucial, as it is hypothesized that there exists a threshold of expression below which cytotoxic T lymphocytes (CTLs) may not recognize the antigen [67,68].

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Box5: The peptide recognized by a cytotoxic T lymphocyte (CTL) on renal cell carcinoma serves as a notable example of an overexpressed antigen, encoded by the MOK (RAGE-1) gene69. RAGE-1 is expressed in a variety of tumors but remains inactive in normal tissues, with the exception of the retina, where low expression is observed. This is due to the retina being an immunologically privileged site and the apparent lack of MHC class I molecule expression in retinal cells. Immunization targeting RAGE-1 could potentially serve as a vaccine against renal cell carcinoma, as it does not express cancer-germline genes [69].

Tolerance to Human Tumor Antigens. Tolerance to Human Tumor Antigens. Tolerance to self-antigens is established in the thymus during T cell development through a series of steps involving positive selection in the thymic cortex. This process retains only those T cells whose T cell receptors (TCRs) can interact with self-MHC [70,71]. Negative selection subsequently eliminates T cells that recognize self-peptides present in the thymic medulla [71]. Consequently, the antitumor T cell repertoire in the periphery is determined by the thymic medulla's ability to process and present tumor-associated antigenic peptides [71]. T cells targeting mutated antigens are not eliminated in the thymus; rather, high-affinity T cells for these antigens persist in the periphery. This phenomenon accounts for the spontaneous antitumor responses to mutated antigens [72].

15. Oncofetal Antigens

Cancer biologists have for many years treasured the similarity between fetal tissues and adult malignant tissues. Oncofetal antigens (OA), [73] are those numerous cellular constituents normally present during embryonic life may also be present during fetal and neonatal life [74].These similar cellular constituents may be present at much poorer concentrations in adult tissues. The most eminent are alpha -1 - fetoprotein (AFP) [75,76], tissue polypeptide antigen (TPA) [77], fetosulfoglycoprotein (FSA) [78], pancreatic oncofetal antigen (POA) [79], and carcinoembryonic antigen (CEA) [80], trophoblast glycoprotein precursor [81] and immature laminin receptor protein which is also known as oncofetal antigen protein [82]. Against several types of cancers oncofetal antigens are promising targets for vaccination.

AFP [75,76] is the major foetal serum protein and resembles albumin, which replaces it shortly after birth. AFP synthesis happens inside foetal liver and passes into the amniotic fluid (AF). A small amount crosses the placental membranes into the maternal circulation. Elevated level of AF/AFP indicate foetal death or one of several abnormalities. Maternal serum AFP measurement can be used as a screening procedure to identify neural tube defects. Only in state of pregnancy AFP is present in females physiologically while generally among humans, AFP is commonly used to diagnose hepatocellular carcinoma and predict its prognosis [75,76,83].

Carcinoembryonic antigen (CEA) is a glycoprotein located on the surface of certain cells, produced by the gastrointestinal tract during embryonic development. Postnatally, CEA is typically produced in minimal quantities, resulting in low serum levels unless specific malignancies are present. In non-smoking adults, the normal CEA range is <2.5 ng/ml, whereas for smokers, it is <5.0 ng/ml. CEA serves as a tumor marker for gastrointestinal cancers, and elevated preoperative CEA levels are expected to normalize following surgical excision of the malignancy. An increasing CEA level may indicate disease progression or recurrence. Additionally, CEA can be elevated in cancers of the pancreas, stomach, breast, lung, medullary thyroid carcinoma, and ovarian cancer. Certain benign conditions, such as smoking, infections, inflammatory bowel disease, pancreatitis, and liver cirrhosis, may also elevate CEA levels. Chemotherapy and radiation therapy can temporarily increase CEA levels due to tumor cell death and subsequent CEA release into the bloodstream. It is imperative to correlate changes in CEA levels during cancer treatment with clinical outcomes [80,84,85].

POA is an oncofetal antigen found in human fetal pancreas, pancreatic tumor tissue, and sera from patients with pancreatic cancer [79]. POA serves as a significant marker in the diagnosis of pancreatic cancer [86]; however, elevated levels of POA have also been detected in the serum of some

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patients with cancers of the stomach, lung, colon, or liver, as well as in the serum of certain pregnant women and individuals with specific benign conditions [87,88]. Consequently, POA can be utilized in conjunction with other assays of various tumor markers to enhance the diagnostic accuracy for pancreatic cancer.

TPA is a pan-carcinoma marker that belongs to the class of cytoskeletal proteins known as cytokeratins or intermediate filaments, which are present in all normal epithelial cells and the cells lining ducts and their sacs [77,89]. Consequently, TPA is expressed by various tumors originating from different organ sites and is released into the serum due to cell destruction. TPA assays represent the first-generation cytokeratin tumor marker tests [90], whereas CYFRA 21-1 is a second-generation monoclonal immunoassay that detects 21-1 fragments of cytokeratin [19]. Cytokeratin markers are appropriate for monitoring rather than diagnosing patients and are frequently used in conjunction with other organ-specific tumor markers [91]. Elevated levels of TPA have been observed during the last trimester of pregnancy and in benign diseases affecting the lung, liver, stomach, and pancreas [92].

Figure 7. ONCOFETAL ANTIGENS [85,91].

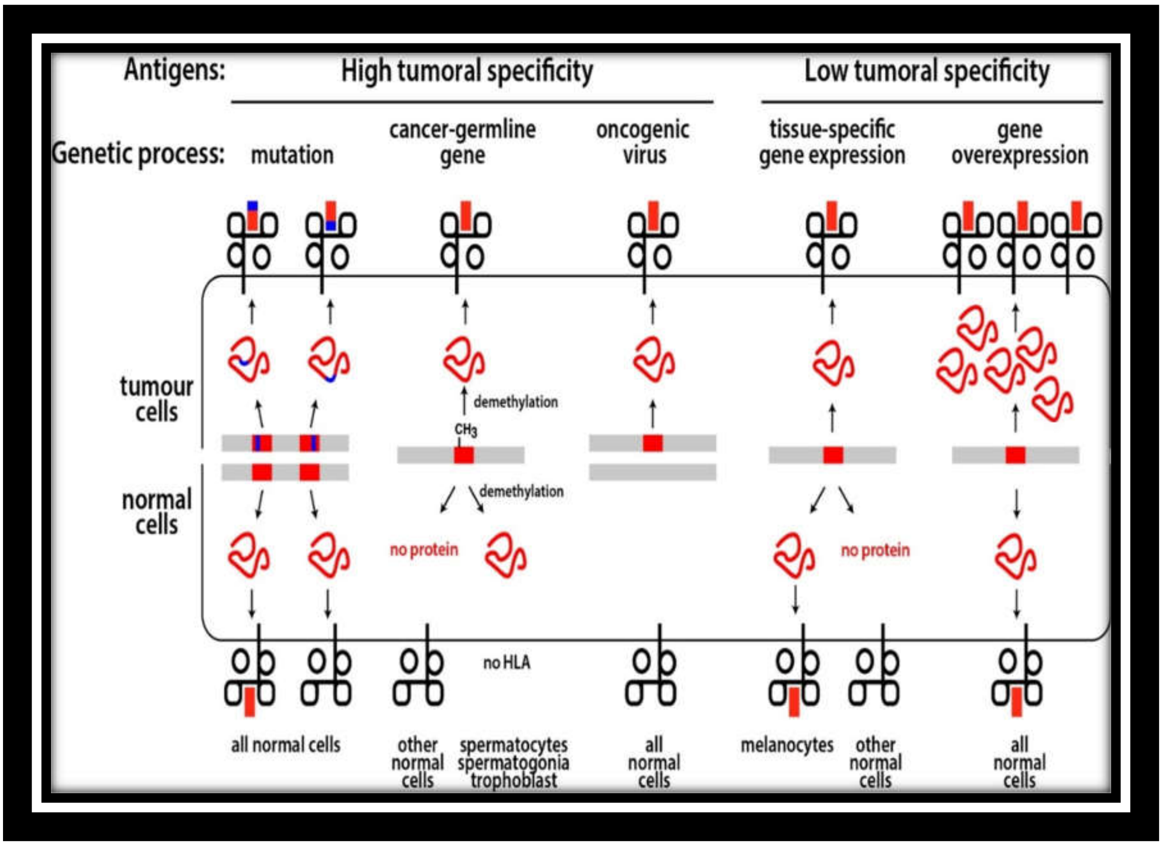

Figure 8. CLASSES OF HUMAN TUMOR ANTIGENS RECOGNIZED BY T LYMPHOCYTES, WITH THEIR GENETIC PROCESS [49].

16. Immune Checkpoints

The immune system employs "immune checkpoints" to avert self-destruction, typically concluding immune responses following the activation of T-cells by antigens. The discovery and therapeutic modulation of key immune-regulatory molecules (checkpoints) at the interface between immune effectors and the tumor microenvironment [93,94] represent significant breakthroughs of their time [17]**. STIMULATORY CHECKPOINTS**

A panel of activator signals orchestrates and regulates the induction of effective adaptive and innate immune responses [95]. Various co-stimulatory molecules, which are often transiently expressed following initial TCR activation, also play a crucial role [96]. These co-stimulatory molecules belong either to the immunoglobulin superfamily or to the TNF receptor (TNFR) family.

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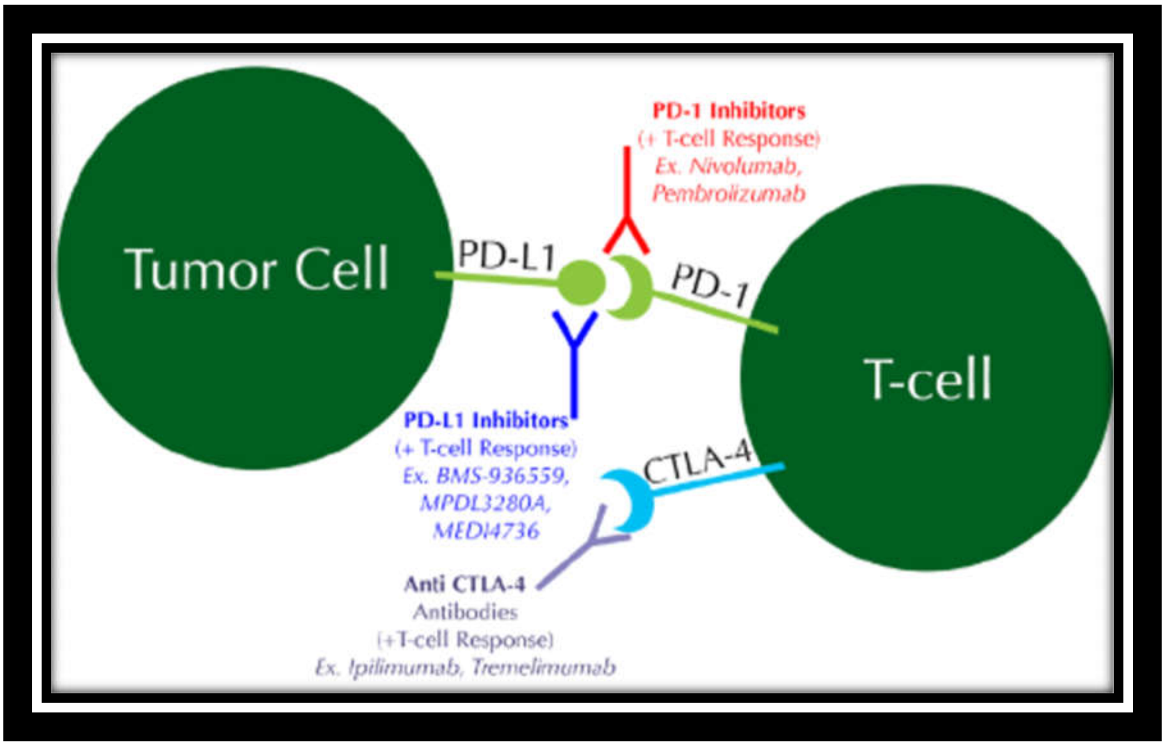

Figure 9. checkpoints [49].

Table 2. STIMULATORY CHECK POINTS [95,96].

	TYPE	LIGANDS	EXPRESSION	FUNCTION
ICOS	CD28 family of B7 binding proteins	B7-H2	enhanced upon T cell activation	Cell Signal, Cell Recognition
OX40	type1 transmembrane receptor	OX40-L	APCs,NK, MastT, activated lymphocytes	Memory response, cytokine production
GITR	Member of TNFR family	TNF superfamily	Tregs, CD8 and CD4 lymphocytes	Inhibit suppression of T regulatory cells
CD137	cell-surface glycoprotein	TNF	activated T lymphocytes (CD4+, CD8+), NK,macrophages, B cells	cell proliferation, activation, survival and IL-2 production
CD40	member of TNF receptor family	CD40L or CD154	expressed on APC, macrophages, B lymphocytes	inducing macrophages, cytokines secretion and activated T helper cells
CD27-CD70	Member of TNF family	CD70	activated lymphocytes and mediating B cell activation	Immunoglobulin production
Glucocorticoid-induced TNF receptor-related gene (GITR)				
ICOS: Inducible T cell co stimulator				
CD: Cluster of Differencition				

Table 3. INHIBITORY CHECKPOINTS [95,96].

	TYPE	LIGANDS	EXPRESSION	FUNCTION
LAG-3	membrane receptor	MHC11	activated T lymphocytes and Tregs	enhance the suppressor activity of Tregs matuaration and activation of DC

TIM-3 / HAVCR2	Protein	galectin-9 (Gal-9), phosphatidylserine (PtdSer), high mobility group protein B1 (HMGB1), and carcinoembryonic antigen cell adhesion	IFNγ, innate immune cells (dendritic cells, NK cells, monocytes)	functional inhibition and apoptosis in T cells, enhance immune-suppressive activity of Tregs.
TIGIT	Receptor protein	lectins CD155 and CD112	T lymphocytes and NK	inhibitory signals
PD1/ CD279	Cell surface receptor that belongs to the immunoglobulin superfamily	PDL1, PDL2	T cell, Pro B cell	prevents autoimmune diseases, promotes apoptosis
(LAG-3) - Lymphocyte activation gene 3				
(TIM-3) - T-cell immunoglobulin- and mucin-domain-containing molecule 3/ **Hepatitis A virus cellular receptor 2 (HAVCR2)**				
(TIGIT) - T cell immunoglobulin and ITIM domain				
(PD1)- **Programmed cell death protein 1**				

18. Immunoediting /Immunesurvillence System

The concept of cancer immunoediting came into existence in the year2002 [97],it is an umbrella process which includes finding of conflict with the immune-surveillance hypothesis. Occasionally, the immune system may facilitate, rather than inhibit, the progression of tumors that possess the ability to evade immune detection. Cancer immunoediting happens under 3 phases which are designated the 'three E's': **E**limination (immunosurveillance), **E**quilibrium (quiescent state) and **E**scape (immune evasion) [98].

Cancer immune surveillance a significant host protection process which inhibits cancer formation and maintains cellular homeostasis. Here immune system works in dual manner as it plays opposing roles for both protecting body from tumor development however promoting tumor progression [99] also.

19. Elimination

The concept of elimination is a fundamental aspect of cancer immune surveillance, crucial for the effective suppression of emerging tumor cells. The course of elimination includes innate and adaptive immune responses against tumor cells [100], with several immunity cells and cytokines secretions come into action during this course of elimination [101].

Among neonates, tumor cells can initially be eliminated by immune checkpoint cells, such as NK cells [102], and through the secretion of IFN-γ in an innate immune response [103]. The elimination of transformed cells leads to immune selection and adaptation, which induces tumor variations and reduces immunogenicity, thereby rendering them resistant to immune effector cells during the equilibrium phase. The phases of the elimination are as follows-

(1) ***Tumor cell recognition*:** Innate immunity is capable of recognizing and attacking tumors. When a solid tumor exceeds a size of 2–3 mm, it necessitates a blood supply to facilitate its progression, which in turn leads to induction of pro-inflammatory signals followed by recruitment of innate immune cells in the form of NK, NKT, γδ T cells, macrophages and DCs at tumor site [104–106].

(2) ***Maturation and migration of DCs, cross-priming for T cells*:** IFN-γ induces apoptosis by exerting cytotoxicity through anti-proliferative and anti-angiogenic effects [107]. Some chemokines originating from tumors and adjacent non-tumorous tissues inhibit angiogenesis [108], thereby facilitating tumor cell death. Necrotic tumor cells are phagocytosed by immature dendritic cells

(iDCs), which subsequently mature under pro-inflammatory conditions and migrate towards tumor-draining lymph nodes (TDLNs) [109].

(3) ***TA-specific T cell generation***: IL-12 [110] and IFN- γ [111] mediated killing of tumor cells is done by NK cells and macrophages, with parallel activation of various cytotoxic mechanisms via perforin, TNF-related apoptosis and reactive oxygen [112] etc. The migrated DCs in TDLNs present TAs to new CD4+ T cells and that results development of TA-specific CD8+ T cells that promotes clonal expansion [113,114]. Tumor antigen-specific CD4+ and CD8+ T cells are recruited to the primary tumor site [114]. The cytotoxic T lymphocytes (CTLs) eradicate the remaining tumor antigen-expressing tumor cells and also select for tumor cells with diminished immunogenicity [115].

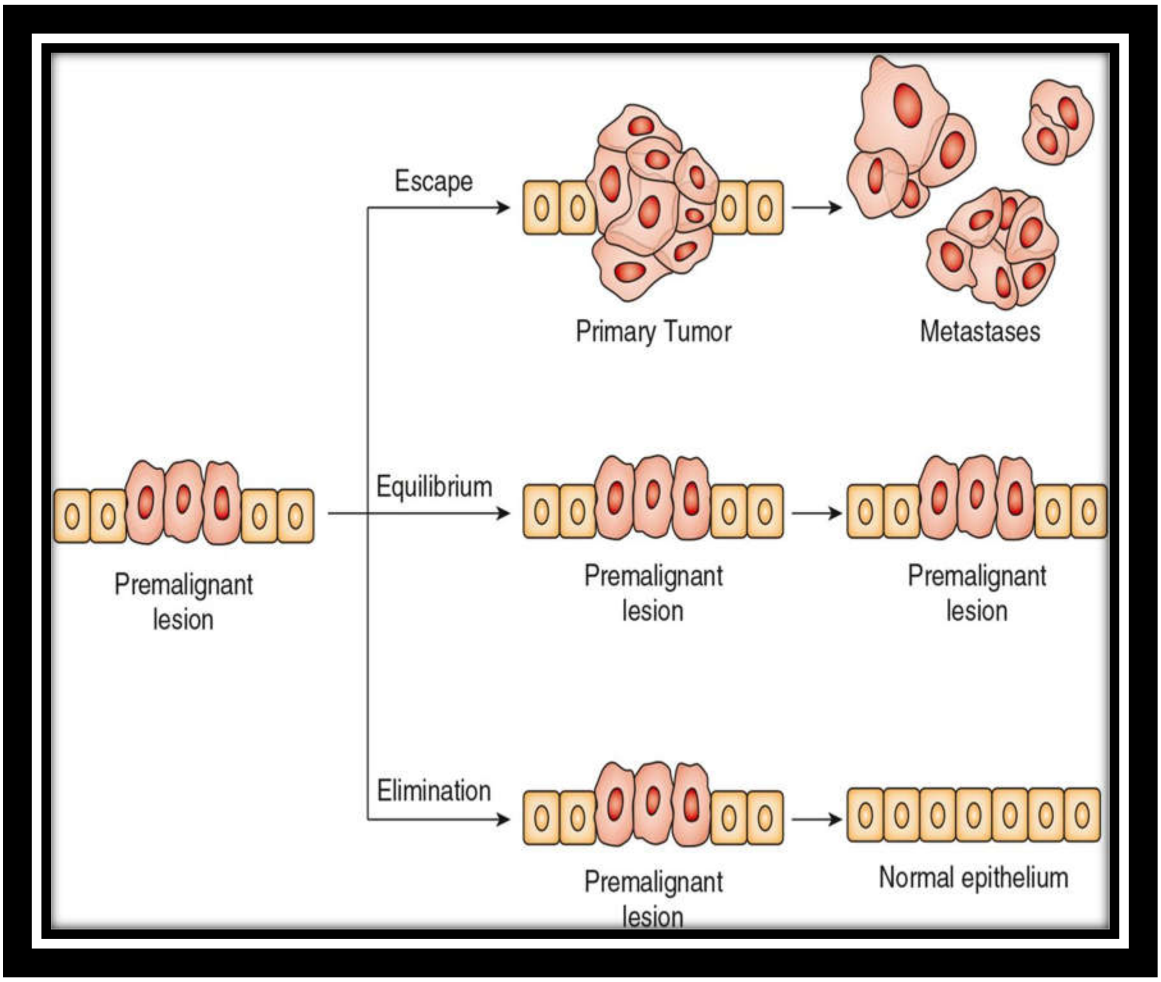

Figure 10. Process of immunosurvillence system [49].

20. Equilibrium

The subsequent phase in the immune editing mechanism is equilibrium, characterized by the continuous elimination of tumor cells, resulting in the emergence of cells resistant to immune responses [116]. This equilibrium process facilitates the immune selection of tumor cells with diminished immunogenicity [116]. Such tumor cells can persist in an immunocompetent host, elucidating the paradox of tumor development in immunologically intact individuals [116,117]. Random genetic mutations occurring within tumors contribute to the formation of more unstable tumors. These tumor cell variants exhibit reduced immunogenicity, and the proliferation of tumor cell clones with a non-immunogenic phenotype is favored by the immune selection process [118,119]. Highly immunogenic tumors, such as those induced chemically or virally, are eradicated by T cells [119,120]. Conversely, the immune selection process promotes the adaptation, survival, and growth of less immunogenic tumor variants within the tumor microenvironment [120]. Given that the

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equilibrium phase involves the ongoing elimination of tumor cells and the generation of resistant tumor variants through immune selection, it is posited that equilibrium is the most prolonged of the three processes in cancer immunoediting, potentially spanning several years [121]. In this context, lymphocytes and IFN-γ play a pivotal role in exerting immune selection pressure on tumor cells [122]. Numerous tumor variants originating from the initial tumor are destroyed, while new variants emerge, harboring distinct mutations that enhance resistance to immune attack [122]. Equilibrium model persists for a long time in the interaction between cancer cells and the host, therefore organ transplantation may provide ground for the transmission of cancer [123]. An interesting report is documented on metastatic melanoma two years later the transplantation among two patients of renal transplants getting kidney from the same donor [124] who was previously treated for melanoma 16 years prior and was considered healthy [124]. Another report states about a recipients of allografts from those considered as healthy donor [125]. It is justified that transmitted cancers may have been kept in equilibrium in the donor and possibly activated by the continuous administration of immunosuppressive drugs that induce and promote the growth of cancer [125].

21. Escape

The phenomenon wherein the immune system fails to effectively inhibit tumor cell proliferation is complex, involving multiple escape mechanisms.

1. Tumor cells may evade immune recognition by reducing antigen presentation [127].

2. The immune system can be suppressed through the expression of receptors such as PD-1, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and lymphocyte-activation gene 3 (LAG-3), among others. Additionally, the production of proteins that enhance tumor cell resistance and survival, as well as cytokines that promote angiogenesis, contribute to immune suppression [128].

3. Alterations in signal transduction molecules are also significant. The recognition of tumor antigens by the immune system is crucial. The loss of the signal transducer CD3-ζ chain in tumor-infiltrating lymphocytes (TILs) has been linked to immune evasion, facilitated by immunosuppressive cytokines and local impairment of TILs [129]. This loss of CD3-ζ is associated with elevated levels of IL-10 and TGF-β, and a reduction in IFN-γ [130]. T-cell receptor (TCR) signal transduction, through the formation of the CD3 complex, is vital for initiating a successful immune response, as well as for tumor antigen expression and T helper 1 polarization [130].

4. ***Tumour-derived soluble factors*-**Tumors evolve escape mechanisms, creates a selective pressure in the tumor microenvironment that can tumor to malignant progression [131]. Factors like vascular endothelial growth factor (VEGF) [132], IL-10 [133], Transforming growth factor beta (TGF-β), [133,134]prostaglandin E2 [135], soluble phosphatidylserine [136] are variety of factors contribute to the appearance of complex local and regional immunosuppressive networks. The secreted factors have the capacity to extend immunosuppressive effects to local lymph nodes and the spleen, thereby facilitating invasion and metastasis despite being deposited at the primary tumor site [136].

Immunological ignorance and tolerance- Immunological ignorance and tolerance: Tumor cells may elicit a protective cytotoxic T-cell response when introduced as a single-cell suspension [137]. However, when transplanted as small tumor fragments, tumors tend to proliferate due to modulation of tumor antigen levels within the tumor microenvironment [137,138]. Tumor cells are encircled by non-tumor cells, including immature dendritic cells (iDCs), fibroblasts, endothelium, and the extracellular matrix (ECM) [139]. The ECM stabilizes tumor antigens [139], while fibroblasts and endothelial cells compete with dendritic cells for the antigen, leading to the down-regulation of many tumor antigens, thereby facilitating tumor growth [139]. Additionally, stromal cells elevate interstitial fluid pressure within the tumor, enabling evasion from immune attack by effector cells [140]. In such scenarios, insufficient levels of tumor antigens are largely overlooked by T cells [140]. Furthermore, iDCs activate CD4+ CD25+ regulatory T cells, which inhibit T-cell activation [141]. Adequate levels of tumor antigens are necessary to elicit an immune response, mediated by mature dendritic cells presenting tumor antigens to T cells through cross-priming [142]. iDCs inhibit the maturation of DCs and T-cell activation, resulting in immunological tolerance [143]. Thus, mediation of immunological

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ignorance as a result of decreased levels of tumor antigen and immunological tolerance because of inhibition of T-cell activation by iDCs [143].

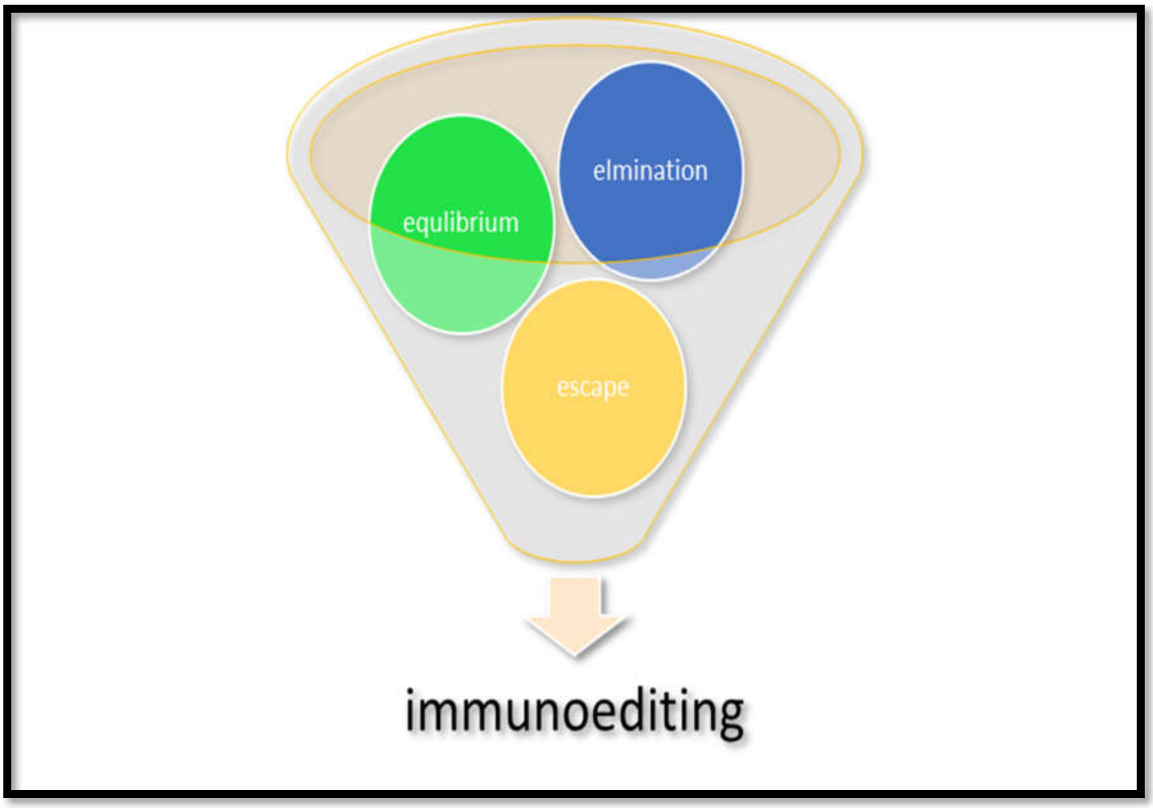

Figure 11. immunoediting system [49].

22. Cancer Skills of Survival

1. **Down-regulation**- Scattered tumour cells can become invisible from T cells by down-regulating MHC Class I molecules and CD8+ T cells cannot recognize them [144] without MHCs. An illustrative case is the suppression of interferon regulatory factor 7 in breast carcinoma, which leads to a reduction in MHC molecule expression on tumor cells, thereby facilitating immune evasion and promoting bone metastasis. [145]

Prevention technique- Tumors can evade destruction within the circulatory system by avoiding binding to circulating immune natural killer (NK) cells. This evasion is facilitated through the reduced expression of adhesion proteins necessary for effective tumor-immune cell interactions. A decrease in Major Histocompatibility Complex (MHC) Class I expression is indicative of "missing self," which prompts NK cells to target these tumor cells by releasing cytotoxic granules. [145]

NKG2D receptor- The NKG2D receptor is an activating receptor located on the surface of natural killer (NK) cells. It is expressed by cells under stress, during infection, or in tumor cells. The binding of an NKG2D ligand to this receptor activates NK cells, leading to the destruction of the stressed cell [147].

> Box6: Numerous ligands of NKG2D have been demonstrated to correlate with enhanced patient survival in cases of colorectal and early-stage breast cancer. Conversely, in high-grade invasive breast and ovarian cancer, these ligands have been associated with a poor prognosis [147].
>
> It shows ***NKG2D is controversial***.

2. **Shielding mechanism-** Cancer cells manifest coagulation response to prevent themselves from immune attack.

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a) *Platelets* An increase in platelets enhances the survival probability of circulating tumor cells by obstructing natural killer (NK) cells. It is hypothesized that platelets form a physical barrier, akin to a shield, between circulating cancer cells and NK cells, thereby preventing direct contact and enabling NK-mediated cell lysis [148].
b) *Tissue factor (TF)* – It is regulator of coagulation and play a role on several levels in the metastatic cascade1 as TF favours angiogenesis promotes tumor cell migration and survival of circulating cancer cells through increasing the above-mentioned platelet directed limitation of NK cells [149].

Tregs- Regulatory T cells (Tregs) facilitate metastasis by inhibiting the activity of cytotoxic CD8+ T cells and natural killer (NK) cells within the primary tumor. Additionally, they impede the function of circulating CD8+ T cells and NK cells against metastatic cancer cells in circulation. Consequently, the reduction of Tregs in primary tumors has been a vigorously pursued therapeutic objective [150].

3. **Tyrosine isomers-** Tyrosine isomers, produced by the primary tumor, inhibit the proliferation of disseminated cancer cells by blocking the MAP/ERK pathway and inactivating STAT3. Consequently, cancer cells are driven into dormancy in the G(0) phase, thereby allowing more nutrients to support the high metabolic rate of the tumor [151].

Box 7 The MAPK/ERK pathway, also known as the Ras-Raf-MEK-ERK pathway, comprises a series of proteins involved in the cellular communication cascade that transmits signals from a receptor on the cell surface to the DNA within the cell nucleus [151].
Upon the binding of a signaling molecule to the cell surface receptor, a series of signal transduction events ensues, ultimately leading to the expression of a protein by the DNA, which facilitates cell division. This pathway encompasses various proteins, including MAPK (mitogen-activated protein kinases) and ERK (extracellular signal-regulated kinases) [151].

23. Immunotherapy

Immunotherapy is characterized by its interaction with the immune system, with the objective of treating or curing cancer. The immune system can identify cancer cells through two primary mechanisms: by recognizing tumor-specific antigens or mutations [152,153], and by detecting differentially expressed molecules in cancer cells compared to normal cells, known as tumor-associated antigens. Immunotherapy represents a promising and progressive treatment option for cancer due to its selectivity, sustained effects, and demonstrated improvements in overall survival and tolerance [152].

BOX8: High-dose interleukin 2 (HD IL-2) has been shown to mediate a long-term and complete response in patients with advanced melanoma and renal cancer [154]. Phase II clinical trials involving HD IL-2 have demonstrated complete disease regression with mild side effects. The FDA has approved HD IL-2 for the treatment of renal cancer and melanoma, thereby establishing immunotherapy as the latest standard for cancer treatment [155].

Historically, cancer treatment has been supported by three primary modalities: surgery, chemotherapy, and radiotherapy. However, immunotherapy has recently emerged as a fourth foundational approach, specifically targeting cancer. Within the realm of immune oncology, three distinct therapeutic strategies have significantly advanced the field: checkpoint inhibitors [93], adoptive T cell transfer [153], and bivalent antibodies [156]. Monoclonal antibodies function by blocking the CTLA-4 and programmed cell death 1 (PD1) immune checkpoints [157]. Adoptive T cell therapy represents a novel therapeutic strategy, offering a potentially powerful addition to cancer treatment through the infusion of tumor-specific T cells [158].

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24. Active Immunotherapy

The presence of multiple tumor-associated antigens on tumor cells necessitates an adaptive activation of T-lymphocytes by the immune system to target these potential antigenic sites. This process, known as active immunotherapy, is designed to induce and stimulate the individual's immune response [157], with the objective of activating the adaptive immune system in cancer patients to eradicate tumors and prevent their recurrence. The primary effector cells in active immunotherapy are the antitumor cytotoxic T lymphocytes (CTLs), which are tasked with recognizing and eliminating tumor cells [156,158].

25. Passive Immunotherapy

Passive immunotherapy involves the administration of pre-synthesized molecules that can be utilized by the immune system. Examples include the application of non-specific immunomodulatory cytokines such as IFN-α and IL-2, as well as the specific monoclonal antibody [159].

BOX9: Sipuleucel-T160 is the first active cellular immunotherapy approved by the FDA for clinical use in the treatment of prostate cancer. This approach involves the transfusion of the patient's own T-lymphocytes, which have been previously stimulated ex vivo and are currently being evaluated in phase I/II trials as a form of cellular adoptive immunotherapy.

A. Cytokines play a fundamental role in tumor immunotherapy. Interleukin-2 (IL-2) has been employed in the treatment of metastatic melanoma and metastatic renal cell carcinoma. Additionally, interferon-alpha (IFN-α) is approved for the treatment of malignant melanoma.
B. Recombinant IL-2 was used in the treatment of solid tumors including neuroendocrine tumors [159,161]. But in few instances cytokines has been less successful in cancers because of significant toxicity and the controversial influence of a single molecules like TNF-α and IL-6. These molecules suppress tumor growth, but also promote growth of other tumors. Further on, IL-6 may also exert immunosuppression [162]. Other cytokines, such as IL-7, IL-11, IL-12, IL-15, IL-21, IFN-β, and IFN-γ, are also undergoing trials as cancer immunotherapies [159,161–164].
C. Monoclonal Antibodies (MAB) Numerous monoclonal antibodies (MAB) are employed in the treatment of solid malignancies. These MABs specifically target receptors on the surface of cancer cells, binding to them and inhibiting the intracellular signal cascade, thereby preventing further tumor growth or reproduction. Notable examples include cetuximab, an antibody against the Epidermal Growth Factor Receptor (EGFR antibody), and trastuzumab, which targets the Human Epidermal Receptor type 2 (HER 2) [166–168].
D. Programmed cell death (PD-1/PD-L1) pathway - The interaction between PD-1 and PD-L1 is a key mechanism used by cancer cells to evade immune surveillance. The PD-1 pathway plays a role in reducing unnecessary or excessive immune responses, including those that are autoimmune in nature. Activated T cells responsible for expression of PD-1, mediate immunosuppression PD-1 functions along peripheral tissues [169]. T cells encounter the immunosuppressive PD-1 ligands, PD-L1 and PD-L2, which are expressed by tumor cells and stromal cells. Inhibition of the interaction between PD-1 and PD-L1 enhances and activates T cell responses in vitro and demonstrates preclinical antitumor activity.
E. PD-L1 works to inhibit T-lymphocyte proliferation, survival and effector functions such as cytotoxicity, cytokine release, and that's how induces apoptosis of tumor-specific T cells. PD-L1 also promote the differentiation of CD4+ T cells into regulatory T cells [169–172].
F. Programmed cell death protein 1 (PD-1) is expressed on T cells, B cells, monocytes, and natural killer T cells following their activation. In contrast, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2) are expressed across a variety of cell types, including non-

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hematopoietic tissues and various malignancies. PD-L1 is expressed at very low levels in non-hematopoietic tissues. The PD-L2 protein is detectably expressed only on antigen-presenting cells (APCs) within lymphoid tissue or chronic inflammatory environments. PD-L2 functions by regulating T cell activation in lymphoid organs, whereas PD-L1 serves to protect healthy tissues from unnecessary T-cell-mediated immune damage. Healthy tissues express negligible amounts of PD-L1, while it is abundantly present in many cancers, acting as a T cell inhibitor. High expression of PD-L1 on tumor cells is an indicator of poor prognosis and survival in cancers such as renal cell carcinoma (RCC), pancreatic carcinoma, hepatocellular carcinoma, and ovarian carcinoma [173,174].

BOX10:Immunotherapeutic approaches as cancer treatment options, include agents
- Immune checkpoint- pathway inhibitors such as anti-cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4) antibody (ipilimumab) [175],
- anti-programmed death 1 (anti-PD-1) inhibitor (pembrolizumab, nivolumab, pidilizumab) [173],
- anti-PD-L1 inhibitors (MPDL3280A, BMS-936559, MEDI4736)

So far, passive immunotherapy has had limited success in the treatment of solid tumors, except in the treatment of malignant melanoma and renal cell cancer (RCC) [173–74].

26. Adoptive T Cell Therapy (ACT)

ACT creates a productive immune response. Harvested from a patient’s blood or tumor, T cells are then stimulated to grow and expand in an in vitro culture environment [175,176]. Once adequately cultured, these cells are reinfused into the host, where they may facilitate tumor eradication. Consequently, this therapy is applicable to the majority of cancer patients, particularly those who do not exhibit an effective anti-cancer response prior to intervention. This therapeutic approach is commonly referred to as chimeric antigen receptor (CAR) T-cell therapy. T-cell activation physically disrupts the proliferation of tumor cells derived from their host, and these engineered cells offer an opportunity to manipulate both the cells and the host in clinical contexts. The efficacy of adoptive cell transfer (ACT) has been enhanced by the incorporation of partial myeloablation prior to the reinfusion of cultured T cells. Through the use of chemotherapy and radiation, cells responsible for peripheral tolerance (T regulatory cells) are temporarily eliminated along with the remainder of the host immune system. For drugs that are unable to specifically target these cells, this approach serves as a more effective method for overcoming host tolerance and has significantly augmented the potency of ACT.

This technique is a cost effective one. ACT is a kind of “new drug” for individual patient, with T cells grown for weeks in labs and patient’s cost of hospitalization to receive it. The specificity of T cells is mediated by MHC control, and each tumor has its own specific set of genomic alterations and mutations that are potentially targeted thereby making it impossible to be exported to the general population [156,157,169–172].

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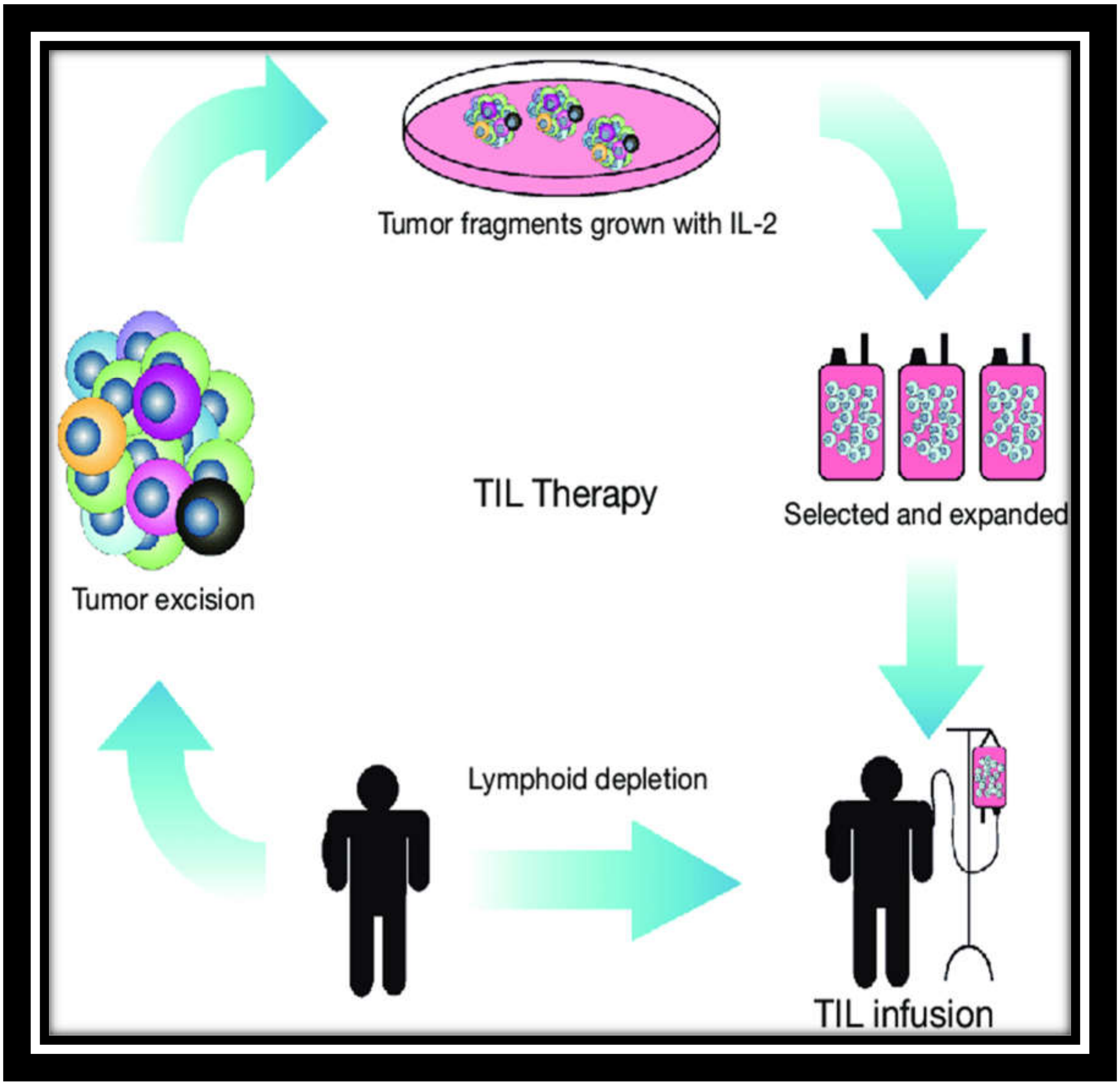

Figure 12. TIL cell therapy [49].

27. Oncolytic Viruses

Oncolytic viruses utilize specially engineered viruses to selectively infect and eradicate tumor cells. These viruses are designed to bypass healthy tissues, targeting specific antigens present on the surface of cancer cells. Upon recognition of these antigens, the virus infects the tumor cell, replicates within it, and ultimately causes cell lysis. This lysis releases antigens, which subsequently activate the immune system to identify and destroy additional cancer cells. Currently, talimogene laherparepvec, or T-VEC, for melanoma, is the sole vaccine approved for cancer treatment. [177–181]

Table 4. In Clinical Trials- Oncolytic Virus [182].

• **Adenovirus:** it is a family of common viruses -causing broad range of typically mild effects including sore throat, fatigue, and cold-like symptoms.
• **Herpes simplex virus:** it can cause the formation of sores on or near the mouth
• **Marabavirus:** found exclusively in insects
• **Newcastle Virus:** it is primarily found in birds; causes mild conjunctivitis and flu-like symptoms in humans
• **Picornavirus:** it can cause a range of diseases in mammals and birds
• **Reovirus:** it can affect the gastrointestinal and respiratory tracts in a range of animal species
• **Vaccinia virus:** used in elimination of smallpox; rarely causes illness in humans

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• **Vesicular stomatitis virus:** member of theMaraba virus family; can cause flu-like symptoms in humans
• **Rubeola virus:** infects the respiratory tract and can cause measles

28. Immune Checkpoint Inhibitors Therapy

Immune checkpoint inhibitors have demonstrated significant promise following their recent approval for the treatment of melanoma, non-small cell lung cancer, and various other malignancies. Monoclonal antibodies are also employed in cancer treatment within the context of immune checkpoint inhibitors [183]. The immune checkpoint proteins, CTLA-4 and PD-1, are receptors expressed on the surface of cytotoxic T-cells that interact with their ligands, cluster differential 80 (CD80)/cluster differential 86 (CD86), and PDL-1 on antigen-presenting cells (APCs), facilitating cancer's evasion of T-cell-mediated cytotoxicity. Immune checkpoint inhibitors function by preventing the binding of these receptors and ligands, thereby disrupting intracellular signaling. These agents have demonstrated improved survival outcomes for adults with solid tumors in clinical trials and have subsequently received approval for the treatment of several diseases, including melanoma [182,184].

Table 5. FDA approved immune checkpoint inhibitors drugs [185].

Drug	**Immune checkpoint target**	**Year of approval**	**Indication**
Ipilimumab	CTLA-4	2011	Unresectable metastatic melanoma
		2015	Adjuvant therapy with Stage III melanoma
Pembrolizumab	PD-1	2014	Advanced or unresectable melanoma
		2015	Metastatic NSCLC with PDL-1 expression and progression on or after platinum therapy
		2016	Recurrent SCCHN
Nivolumab	PD-1	2014	Unresectable or metastatic melanoma with progression after ipilimumab or BRAF inhibitor if BRAF V600 mutant
		2015	NSCLC with progression after or on platinum therapy Metastatic RCC after prior anti-angiogenic therapy
Atezolizumab	PD-1	2015	NSCLC with progression after or on platinum therapy

NSCLC: Non-small cell lung cancer, RCC: Renal cell carcinoma, SCCHN: Squamous cell carcinoma of the head and neck, PDL-1: Programmed death ligand-1, CTLA-4: Cytotoxic T lymphocyte associated-4, PD-1: Programmed cell death protein 1

29. Role of Monoclonal Antibodies in Cancer

Hybridoma technology is currently employed in the production of monoclonal antibodies. Chemotherapeutic monoclonal antibodies (CmAbs) have become standard therapeutic agents for various hematological and solid malignancies in humans. CmAbs were structured and engineered with the aim of specific goals and predicted advantage, thus acting as 'targeting missiles' toward cancer cells. [186–190]

30. Mechanisms of Action of CmAbs

CmAbs target cancer cells by binding to cell surface antigens. Upon attachment to the specific target tumor, cell destruction is initiated through three primary mechanisms: 1) direct tumor cell death by targeting and inhibiting cell survival signaling pathways; 2) induction of apoptosis or direct delivery of cytotoxic drugs or radioisotope modalities via conjugated antibodies; and 3) immune-mediated tumor cell killing by engaging antibody-dependent cell-mediated cytotoxicity, complement-mediated cytotoxicity, and subsequent activation of cellular phagocytosis.

Immuno-stimulatory CmAbs may activate T lymphocyte cells through T lymphocyte inhibitory receptors inhibition. C vascular ablation and disruption of stromal interaction with cancer cells leads to denied blood supply to tumors and supporting network thereby promoting tumor regression [189,191]- [193]

BOX11:Cell surface antigens [23] include antigens associated with growth and differentiation, such as

- CD;egCD20, CD 30, CD 33 and CD52
- CEA
- epidermal growth factor receptor (EGFR),
- receptor activator of nuclear factor kappa-B ligand (RANKL),
- human epidermal growth factor receptor 2 (HER2),
- VEGF, VEGF receptor (VEGFR), integrins (eg$\alpha V\beta 3$ and $\alpha 5\beta 1$),
- fibroblast activation protein (FAP)
- extracellular matrix metalloproteinase inducers [EMMPRIN].

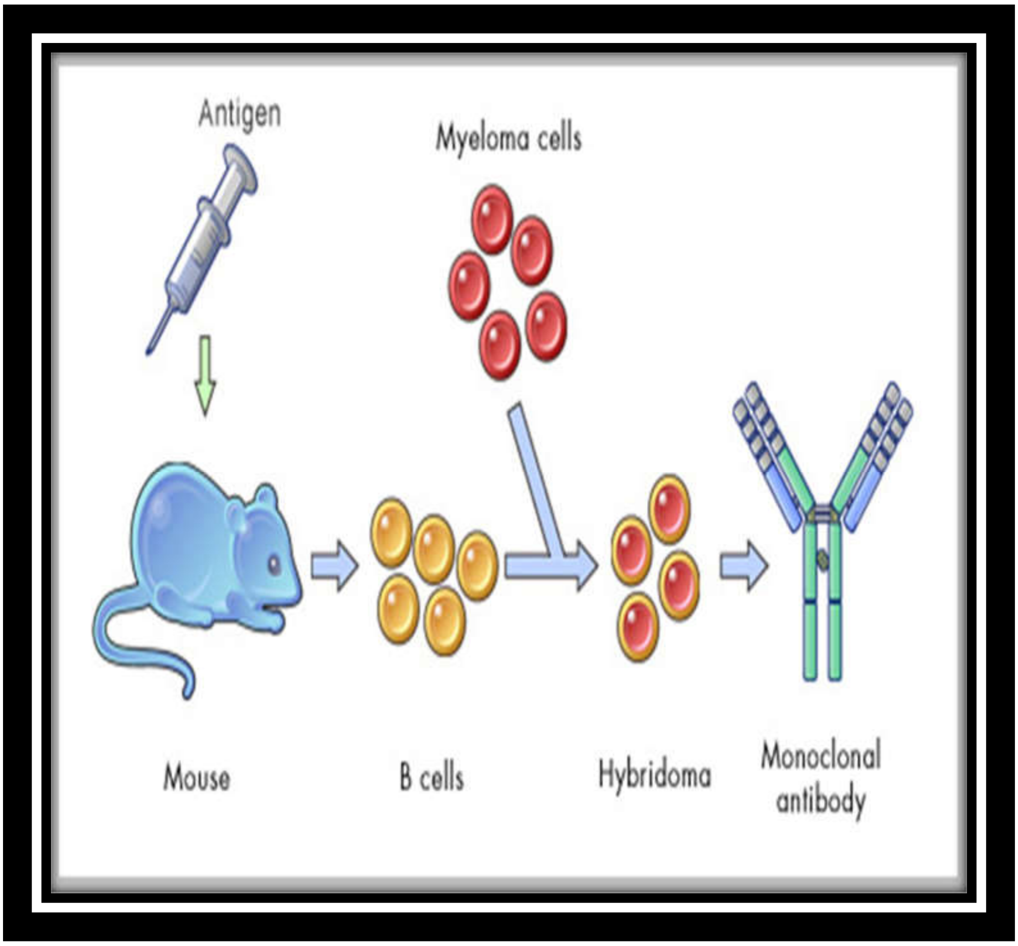

Figure 12. Hybridoma technology [49].

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31. Classification of CmAbs

A. **Murine CmAbs**,- Murine CmAbs, exclusively derived from mice, were the first to be utilized in cancer chemotherapies [194].

B. Chimeric CmAbs were developed with variable regions derived from a murine source and constant regions (65%) from a human source. Various other combinations exist that are non-humanized, including rat-mouse hybrids possessing three distinct antigen-binding specificities: one for tumor cells, one for T lymphocyte cells, and one for accessory cells. A fully human Fc portion of chimeric CmAbs demonstrated reduced immunogenicity and more efficient interaction with human effector cells and the complement system compared to murine CmAbs [195].

C. ***Humanized CmAbs*** - Humanized CmAbs are predominantly (90%) derived from human sources, with the exception that the complementarity-determining regions of the Fab portion of these antibodies are of murine origin. Consequently, they exhibit even lower immunogenicity compared to chimeric CmAbs [196,197].

D. ***Human CmAbs*** - Human CmAbs, which are entirely human and derived from transgenic mice antibodies, exhibit superior affinity values toward human antigens when compared to chimeric and humanized CmAbs. Additionally, they demonstrate minimal or no hypersensitivity responses [198].

E. ***CmAbs conjugated-*** The conjugation of CmAbs facilitates a targeted approach to tumor cells while minimizing systemic toxicities to normal cells. There are three categories of conjugated CmAbs: Radiolabelled CmAbs, which are linked to radionuclide particles; Chemolabelled CmAbs, which are attached to anti-neoplastic drugs; and Immunotoxin CmAbs, which are associated with plant and bacterial toxins [184].

32. Limitations of CmAbscompared with Conventional Chemotherapy

- The adverse effects of unconjugated CmAbs are usually mild.
- Conjugated CmAbs precipitate severe adverse effects, hypertension and kidney damage. Most commonly CmAbs can have chills, weakness, and headache, nausea, diarrhoea, hypotension and rashes as side effects.
- Production cost estimated is twice that required for conventional drugs

33. Nanomedicine in Cancer Therapy

Traditional chemotherapy, which employs various chemotherapeutic agents either individually or in combination, encounters several challenges. These include severe adverse effects in patients due to the unintended retention of drugs and metabolites in vital organs [199]. Additionally, the efficacy of the administered drug may be compromised due to the development of multidrug resistance by cancer cells. These detrimental outcomes often lead to suboptimal therapeutic results and a high rate of recurrence [187]. In contemporary times, nanotechnology has garnered significant interest from researchers across various disciplines for the development of materials with diverse compositions and properties that are compatible with biological environments. Research in this area has led to the creation of a wide array of innovative nano-biomaterials with engineered characteristics and optimal functions, including supramolecular structures, nanocrystal growth, and sol-gel chemistries. The application of nanotechnology in medicine has generated substantial interest in cancer therapies and diagnostics by producing materials with controlled multi-dimensional (1–3 D) structures at the nanoscale, approximately 1–100 nm in one of the measurable dimensions, for drug/gene delivery and diagnostic probes for radioactive or other advanced therapeutic strategies. These engineered materials, as drug delivery platforms, hold great promise in providing controlled release of drugs, genes, or therapeutic peptides with enhanced efficacy and safety. Compared to traditional chemotherapeutic agents, these platforms exhibit responsiveness to the cancer microenvironment for drug release, including photothermal therapy, photodynamic therapy, ultrasound responsiveness, and immunotherapy, among others. Some of these have been approved for cancer therapy, while numerous others are undergoing clinical trials [200–202].

34. Advantages

1. The encapsulation of diverse range of therapeutic materials such as drugs, genes or therapeutic peptides requires high surface-to-volume ratio of nanoparticles and surface coating of therapeutic agents happens through physical adsorption or electrostatic interactions.
2. The availability of abundant functionalization surfaces facilitates the ease of restraining therapeutics guests, and various bio-macromolecules for fluctuating their behaviour in vivo.

35. Types

Based on the chemical composition three major divisions of nano medicine are organic, inorganic, and hybrid systems [203].

A. Liposomes, emulsions etc are certain carbon based organic substances are quiet compatible and may degrade in physiological environment, for example, Abraxane, Doxil, DaunoXome, and,Myocet. But they have poor stability in the physiological fluids and deprived drug encapsulation efficiency [204,205].

B. With exceptional thermal and colloidal stabilities, the inorganic nanobiomaterials show various qualities like resistance with structural and chemical optical features, tailoring architecture. Magnetic nanoparticles, semiconductor quantum dots, metal nanoparticles, layered materials, mesoporous silica materials are few examples of this class. Safety and degradability are two major challenges before these substances in biological environment [206,207].

C. Loaded with desired intrinsic characteristics the hybrid system consists of both organic and inorganic material manifests great potential of compatibility, degradability. The system also capable of stimuli- responsive delivery to the therapeutic guest [208].

The therapy carrier nanoparticles are delivered through intravenous route and are systemically circulated in vivo extensively owing the their tiny size. These tailormade nanoparticles with amplified physiochemical characteristics adhere to different proteins in the circulation prolong the circulation time and this conveniently facilitates their reach to their target tumor site. Further internalization with in cell could be via passive mode or through active targeting process, leading to better and enhanced outcome over conventional therapeutic method. The rate of bioavailability and final internalization depends on size, shape and surface charge of the nanoparticle. These nanoparticle traits play a very integral role which facilitates targeting pathological tissues with safe, effective site specific drug delivery [209–213].

Table 6. BRIEF EXAMPLES OF ORGANELLE-TARGETED NANO-FORMULATIONS IN CANCER THERAPY [214].

Organelle	Composition and Size/nm	Responsiveness	Pathway and Outcome
Endosome/ lysosome	V-ATPase inhibition	Cisplatin	ERK/MEK. Regulating autophagy that assisting in chemoresistance in ovarian cancer
	T-UPSM 37.6±1.9	pH	Lysosomal catabolism inhibition.KRAS mutant pancreatic cancer treatment through simultaneous lysosomal pH buffering and rapid drug release
Mitochondria	TPP-CeO_2 2.2	-	Scavenge mitochondrial ROS efficiently to reduce oxidative stress.Suppression of neuronal death

Nucleus	Chitosan nanoparticles-NLS 25, 150	-	Study on impaired nuclear import and aberrant nanoparticle intracellular trafficking in glioma. Effect of nanoparticle size and NLS density on nuclear targeting in cancer and normal cells
	Acridin-9-Methanol nanoparticles 60	Visible light (≥410 nm)	Nucleus targeted intracellular controlled drug release.Fluorescent imagine and killing the cancer cells
Golgi apparatus	PTX–CS–RA 192.7±1.8	pH	Loss of cystic structure Enhancement of antimetastasis combined with chemotherapy
Ribosome	Dd-mrp4	-	p53- or RB-like functions Ectopically expressed Dd-mrp4 suppressing the cell proliferation through inducing apoptotic cell death
Abbreviations: Dd-mrp4, Dictyostelium mitochondrial ribosomal protein S4; PTX-CS-RA, Retinoic acid-conjugated chondroitin sulphate loading with paclitaxel; TPP, triphenylphosphonium; T-UPSM, Triptolide prodrug-loaded ultra-pH-sensitive micelles. NLS, Nuclear localization sequence			

36. Nanomedicine in Cancer

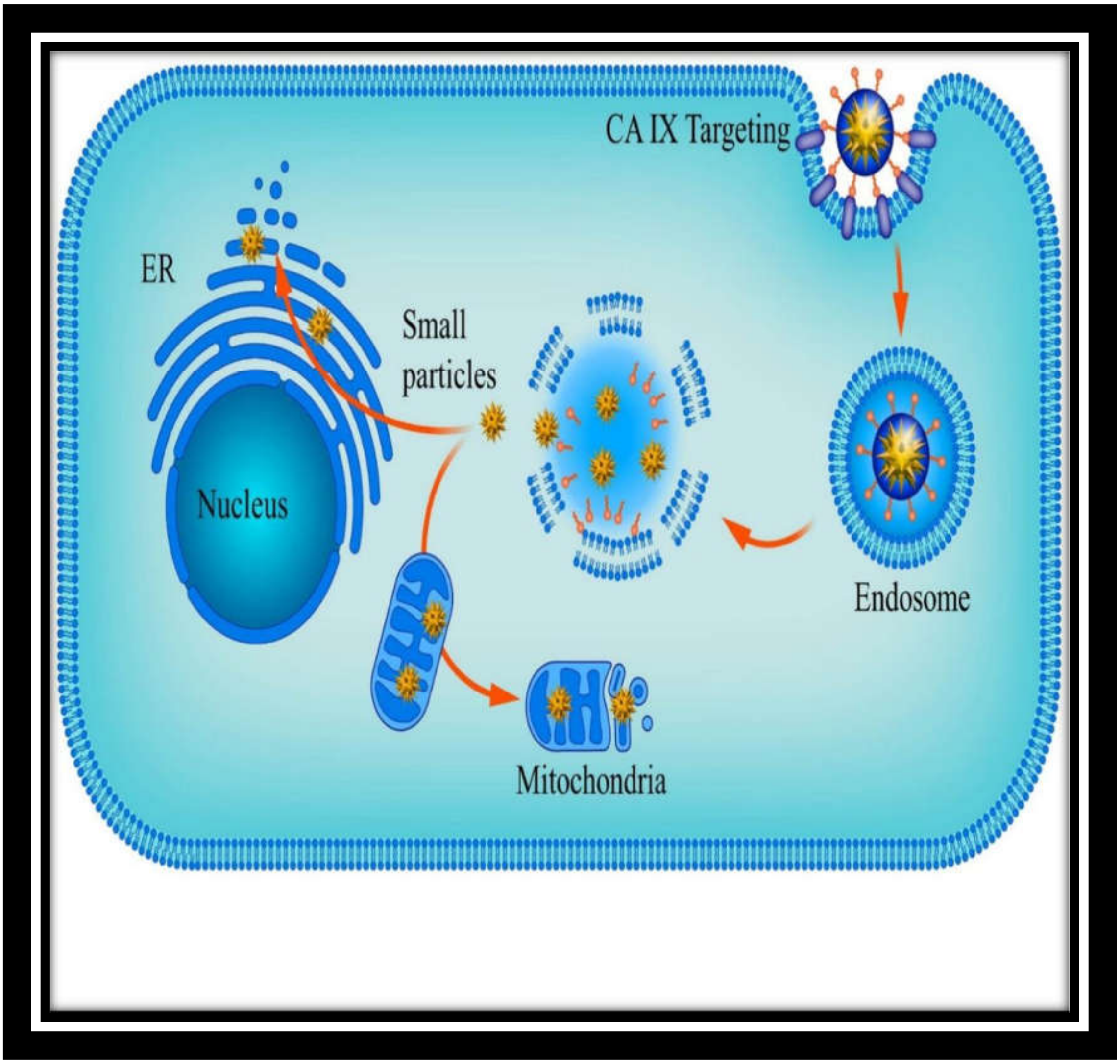

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Figure 13. NANOMEDICINE IN CANCER [49].

Here we have tried to cover all relevant literature of cancer immunity and relatives but, treatments and cancer vaccines, bivalent anti-MET antibodies as therapeutic agents are whole new concepts to be discussed further in other chapters.

37. New Paradigm in Cancer Therapeutics; Cancer Vaccine

The cancer mortality has been drastically reduced worldwide since the development of cancer prevention vaccine, however developing therapeutic cancer vaccines aiming to elicit immune response directly against cancer cells are facing many challenges. Moreover vaccines primarily as monotherapies targeting tumor associated antigens were tested in late stage cancers. While many contemporary vaccines with focus on neoantigen targets have shown evidentiary clinical efficacy when combined with immune check point inhibitors, particularly in precancer and early cancer stage.

Russia's Enteromix [215], a personalized mRNA-based cancer vaccine has proven 100 % efficacy and safety in clinical trials, a potential breakthrough in cancer treatment. Mechanism involves training the immune system to eliminate cancer cells without any serious effects. The vaccine is awaiting final approval from ministry of health to serve in public service.

38. Conclusion

Our potent immune system competent enough to respond strongly to check tumor spread in the body in normal circumstances. Immunotherapy one of the most significant advancements in cancer therapeutics, also with its various modalities associated, the immunotherapy can induce a very strong and effective immune response against cancer. With improvement in our knowledge about mechanistic approach of cancer and cancer therapies led to the discovery of targeted drug design in the form of various biologically active drugs, therapeutic antibodies, vaccines and cell infusion treatment. In past few years CAR-T cell therapy, Immune checkpoint inhibitors (ICIs) and of course vaccine have shown remarkable success in clinical trials. However still many challenges in terms of immune escape, adverse immune response and tumor heterogeneity are prevailing, which limit the efficacy of treatment regimen. In the coming future progress and improvement in immunotherapeutics will promote numerous combination treatment approach involving novel strategies with aim to simultaneously stimulate immune response and to check tumor suppressive mechanism. Tailor made treatment of individual patient on the basis of their genetic, molecular & immune status will surely lead to effective cancer treatment. Future research studies and clinical trials holds promises to meet various persisting challenges. Also integration of AI will prove to be critical step towards improving treatment outcome, efficacy and access to large mass of society.

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