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Strategies employed by tumor cells to evade immune surveillance and immunotherapeutic interventions: A comprehensive review

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Abstract
Cancer, caused by the uncontrolled growth of aberrant cells, is still one of the greatest threats to humanity's health. The relationship between malignancy and immunity has been studied for more than a century, dating back to Rudolph Virchow's definitive emphasis on this relationship over 150 years ago [1]. Three basic principles underlying the basis of this relationship are accountable for the mechanism whereby immunity functions to defend the host: first, the immune response identifies "nonself" antigens of organisms or of infected and transformed cells; secondly, it utilizes selective effector mechanisms to selectively destroy these noxious agents with sparing of the host's own tissues; and, thirdly, through adaptive responses, it acquires immunological memory to render the body resolutely resistant to subsequent insult or repeated challenge [2].
The dynamic interaction between immunity and tumor development has led to the formulation of the immunoediting paradigm, which reflects the delicate balance between immune surveillance and malignant progression in cancer biology [3, 4]. This paradigm is defined by three sequential phases: elimination, where immune mechanisms target and destroy transformed cells; equilibrium, during which residual malignant cells persist in a dormant state under immune control; and escape, whereby tumor cells acquire the capacity to bypass immune defenses, leading to disease progression [4]. The ability of cancer to circumvent immune recognition is now recognized as a defining hallmark of malignancy and serves as the conceptual basis for modern immunotherapeutic interventions. While the earliest attempts at immune-based cancer treatment can be traced back to the pioneering efforts of William B [1, 5]. Coley and his collaborators in the nineteenth century, contemporary research and technological advances have expanded these foundations, giving rise to novel immunotherapeutic strategies aimed at suppressing or eradicating diverse forms of cancer.
These breakthroughs have brought the concepts of immunooncology and cancer immunotherapy into clinical relevance. This review underscores the emerging and evolving discoveries contributing to the comprehension of immunooncology while emphasizing the significance of pertinent immunotherapies as potential interventions in cancer treatments.

Keywords: Immune surveillance, immunotherapeutic interventions, cancer biology, immunoediting paradigm, immune evasion, cancer immunotherapy

1. Introduction

1.1 Overview of tumor biology

Cancer ranks as the second most common cause of mortality in the Middle East, with both its incidence and associated death rates continuing to rise [6]. The development of cancer is strongly associated with diverse genetic alterations, including chromosomal abnormalities, translocations, and modifications in glycosylation patterns. Altered glycosylation, in particular, contributes to tumor heterogeneity by affecting cell proliferation through modifications of growth factor receptors [7]. Such mutations typically involve oncogenes, which drive cell proliferation, or tumor suppressor genes, which function to restrain uncontrolled growth. Beyond genetic changes, epigenetic modifications also play a critical role in tumorigenesis. DNA methylation is a prominent example, where hypermethylation can lead to the silencing of tumor suppressor genes, while hypomethylation may result in the inappropriate activation of genes, thereby promoting malignancy across different tissues and organs [8].
Factors such as hereditary influences, environmental exposures (diet, carcinogens, radiation), and lifestyle choices (smoking) contribute to the initiation of cancer. In many cases, the underlying etiology is linked to inherited or acquired genetic mutations, which shape the

diverse pathways of cancer development depending on the specific organ or tissue involved and the associated molecular or genetic alterations [9, 10]. The terminology used in describing different forms of cancer adds complexity to oncology, distinguishing between primary cancers localized at their origin and secondary or metastatic cancers that migrate to other body locations. It is crucial to note that the terms "cancer" and "tumor" cannot be used interchangeably, with tumors referring to masses of abnormal cell growth that can be benign or malignant [11].

Metastatic cancers, although derived from the same transformed cells as the primary tumor, gradually develop unique traits as the disease progresses. The metastatic cascade begins when certain malignant cells dissociate from the original tumor mass and disseminate via the lymphatic system or blood circulation to distant sites [12]. During this process, metastatic cells release enzymes such as matrix metalloproteinases, which degrade extracellular matrix components and facilitate tissue invasion through intricate signaling networks [13]. Although the majority of circulating tumor cells fail to survive in circulation, a subset can successfully adhere to the endothelial lining of venules or capillaries, enabling their extravasation into secondary organs or tissues. Once established, these metastatic cells often exploit angiogenesis to secure a blood supply that sustains further growth and proliferation. The growth of metastatic cancer relies on a sufficient blood supply for nutrients and oxygenation and efficient removal of cellular waste through angiogenesis [14, 15].

The categorization of cancer types remains complex, owing to the diversity of their origins and biological behaviors. Tumors may arise from different tissues such as the epithelium, mesenchyme, or glandular structures, and are therefore classified as carcinomas, sarcomas, or adenocarcinomas, respectively, depending on their site of origin [16]. Malignancies that develop within the lymphatic system are identified as lymphomas, whereas those arising in the bone marrow, including myeloma and leukemia, disrupt normal hematopoiesis by impairing the production of plasma cells, erythrocytes, or leukocytes [17, 18]. Furthermore, cancer pathophysiology differs markedly between pediatric and adult populations; childhood malignancies are often characterized by rapid progression and increased aggressiveness compared to their adult counterparts [19].

Given the complexity and heterogeneity of cancer pathogenesis, developing specific treatments for each type remains challenging. Significant progress has been made in therapies targeting the six hallmarks of cancer, but a more beneficial approach may involve understanding and targeting a common key player, such as the immune system [20]. Recognizing the critical role of the immune system in oncogenesis is essential for gaining insight into its potential exploitation as a treatment option for cancer.

1.2 Immune system

The immune system consists of a diverse array of soluble bioactive molecules, proteins, cytokines, and specialized cells that collectively form an intricate biochemical network. This coordinated system is responsible for detecting foreign antigens and initiating protective responses to defend the host against them.

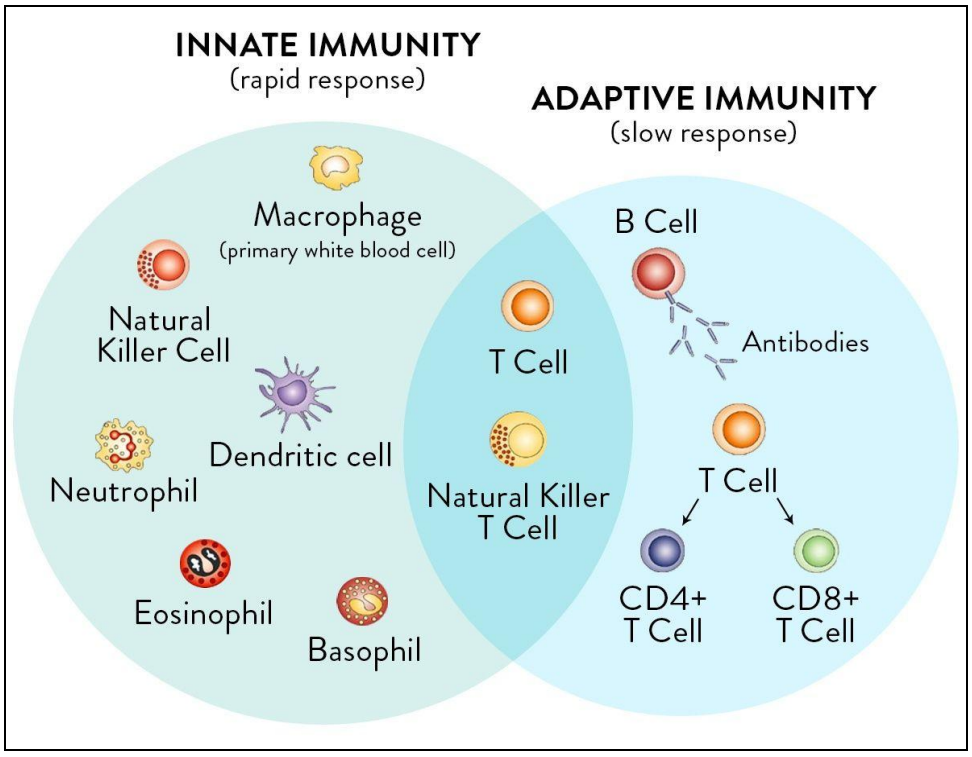

Fig 1: Overview of the immune system: innate and adaptive immunity.

There are two forms of immune responses, innate and adaptive, working to protect the host's normal state of homeostasis. Innate responses are nonspecific and immediate, acting quickly against foreign antigens like pathogenic microbes, allergenic antigens, or non-self proteins. Innate immunity, depicted in Figure 1, lacks the ability to form immunological memory but can still

distinguish between "self" and "nonself" or different groups of pathogens through specific receptors [2, 21].

Phagocytes and natural killer (NK) cells play a crucial role in the immune response. Phagocytes, including neutrophils, monocytes, and macrophages, quickly defend the host by engulfing cells that display foreign antigens or modified self-antigens. This process involves killing the targeted cells using lysosomal enzymes (see Figure 1) [25].

Natural killer (NK) cells represent a critical component of the innate immune system, offering protection through recognition mechanisms involving major histocompatibility complex class I (MHC I) molecules, which are ubiquitously expressed on the surface of all nucleated cells [25]. When target cells display abnormal or diminished MHC I expression-often indicative of cellular stress, transformation, or infection-NK cells respond by releasing cytotoxic molecules such as perforin and granzyme, thereby initiating apoptosis in the compromised cells [25]. In parallel, other innate immune cells, including eosinophils, basophils, and mast cells, contribute to host defense by secreting inflammatory mediators such as chemotactic leukotrienes. These mediators enhance local immune responses by attracting additional immune cells to sites of tissue injury or inflammation, thereby amplifying innate immune activity (Figure 1).

Unlike innate immunity, which provides immediate defense, adaptive immunity is characterized by the generation of immunological memory through highly specific responses directed against antigens [25]. This form of immunity develops progressively, as naïve lymphocytes-particularly T and B cells-differentiate and mature into effector T cells or antibody-producing plasma cells over time, rather than mounting an instant reaction [26]. T lymphocytes can be broadly divided into two groups based on their T cell receptor (TCR) type: αβ T cells and γδ T cells [27]. While γδ T cells represent a relatively small subset, they are notable for their ability to recognize “nonself” molecules via pattern recognition mechanisms independent of MHC-mediated antigen presentation [27]. In contrast, αβ T cells are more abundant and are further classified into CD4+ helper T cells and CD8+ cytotoxic T cells, each playing distinct roles in orchestrating adaptive immune responses [28, 29].

The differentiation of naïve CD4+ T cells into effector subsets requires costimulatory signaling, which occurs through the interaction between major histocompatibility complex class II (MHC II) molecules on antigen-presenting cells-such as dendritic cells, macrophages, and B cells-and the T cell receptor expressed on naïve CD4+ T cells (Figure 1) [28, 29]. The fate of these cells is largely determined by the surrounding cytokine environment and the timing of the costimulatory signal, guiding their maturation into specialized effector subsets such as T helper 1 (Th1), T helper 2 (Th2), or regulatory T cells (Tregs) [29]. Each of these subsets is characterized by the secretion of distinct cytokines that shape and regulate the immune response in specific ways [29].

For example, Th1 cells are characterized by the secretion of interferon-gamma (IFN-γ) and interleukin-2 (IL-2), which play central roles in cell-mediated immunity but are also implicated in the development of autoimmune conditions. In contrast, Th2 cells release cytokines such as IL-4, IL-5, IL-10, IL-13, and IL-31, which are primarily involved in coordinating immune defense against extracellular pathogens and in mediating allergic responses [29]. Regulatory T cells (Tregs) function to suppress excessive immune activity and maintain tolerance by producing immunomodulatory cytokines, including transforming growth factor-beta (TGF-β), IL-35, and IL-10 [29]. In a parallel manner to natural killer (NK) cells within the innate immune system, naïve CD8+ T cells depend on antigen recognition through MHC class I molecules to mature into effector cytotoxic T lymphocytes [28].

2. Immunosurveillance

Ehrlich, in the early 1900s, proposed the concept of immune surveillance, suggesting that a key role of the immune system was to identify and remove tumors within the host (30). As a natural outcome, the occurrence of tumor development is expected to increase under conditions where innate and/or adaptive immunity is compromised or suppressed. This hypothesis has been explored experimentally through the use of knockout mouse models lacking specific components of the innate or adaptive immune system. Supporting this view, mice deficient in perforin, interferon (IFN)-γ, or STAT1-key mediators of interferon signaling-demonstrated a marked increase in both the incidence and progression of spontaneous as well as chemically induced tumors [31]. Further evidence for the role of adaptive immunity in tumor surveillance has been provided by studies using RAG-2-deficient mutant mice [32]. The RAG genes encode DNA repair enzymes essential for the recombination of B-cell receptors (antibodies) and T-cell receptors (TCRs). Notably, mice with homozygous deletion of the RAG-2 alleles, which eliminates the development of NKT cells, T cells, and B cells, displayed a significantly higher frequency and growth of spontaneous tumors in addition to chemically induced malignancies [33].

In humans, these observations are mirrored by the heightened vulnerability to specific types of neoplasms in immunocompromised individuals, particularly those who have undergone organ transplantation and individuals with acquired immunodeficiency syndrome (AIDS) [34, 35].

2.1 Cellular Mediators of Immune Surveillance

2.1.1 Cytotoxic T Cells

T lymphocytes possess the ability to patrol and survey nearly all tissues of the body in search of foreign or harmful elements; thus, both naïve and effector T cells serve as highly dynamic migratory populations that are essential for immune surveillance and the establishment of adaptive immunity against infections and cancer. The differentiation and functional specialization of T cells are tightly regulated by transcription factors, cytokines, chemokines, integrins, and metabolic cues, with T-cell lineages traditionally viewed as stable and mutually exclusive entities [5] (Fig. 1). Among these, cytotoxic CD8+ T cells act as the primary effectors responsible for eliminating infected or malignant cells, while CD4+ T cells play a supportive role by sustaining CD8+ activity and preventing functional exhaustion.

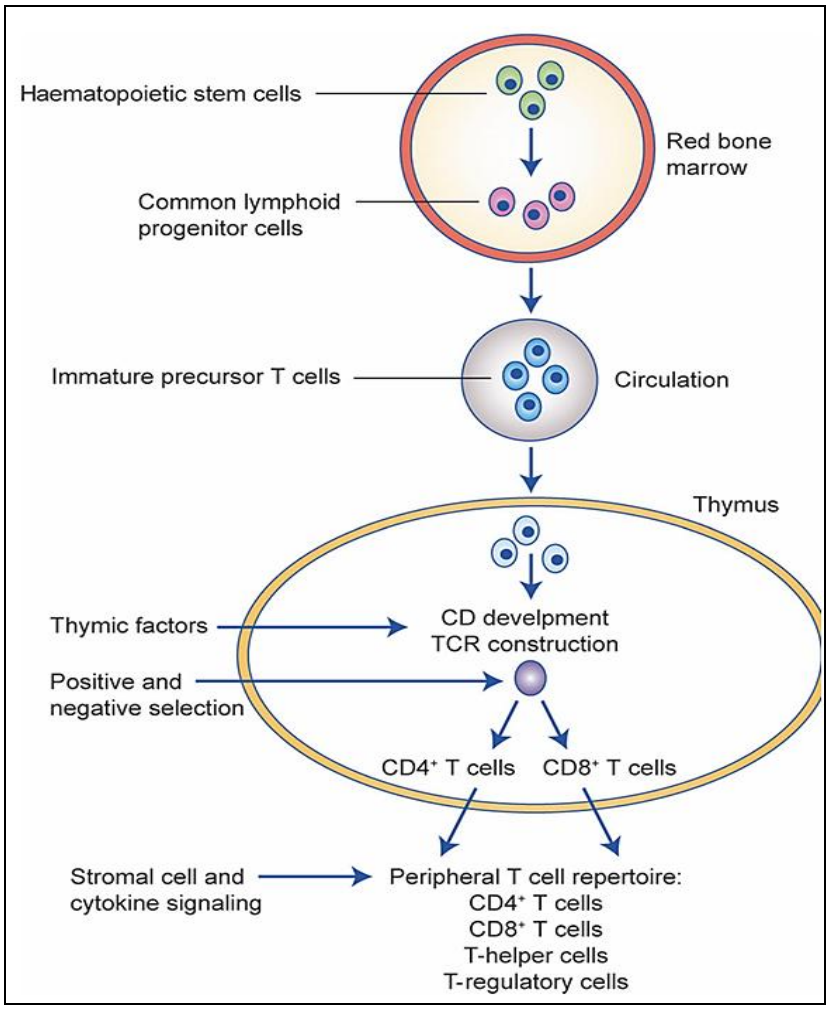

Fig 2: T-cell differentiation-an overview.

T-cell: interactions and activation

CD8+ T cells recognize antigens through interactions with major histocompatibility complex class I (MHC I) molecules [6], which are expressed on the surface of antigen-presenting cells (APCs) and target cells. These molecules present antigenic peptide fragments generated by proteasomal degradation of cytoplasmic proteins, which are displayed within the binding grooves of MHC I complexes [36]. Upon encountering an APC or target cell, CD8+ T cells attach and actively scan the cell surface by crawling across it, a process in which direct physical contact and cellular movement transform mechanical forces into biomechanical signals that are critical for the activation of the T-cell receptor (TCR) complex [37]. In addition, chemokine and integrin gradients guide activated CD8+ T cells toward their targets, where they establish immunological synapses formed between supramolecular activation clusters and adhesion molecules-such as intercellular adhesion molecules-on the surface of target cells [8]. To verify the identity of the target, the TCR engages the presented peptide while CD8 functions as a co-receptor by binding to the MHC-α subunit. Following this recognition event, a secondary co-stimulatory signal delivered through the CD28 receptor is required to fully activate the cytotoxic machinery of the CD8+ T cell [38].

Target-cell death

Interactions between CD8+ T cells and their targets are marked by the continuous motility of the T cell across the surface of the target. As described earlier, these mechanical forces facilitate the formation of pores in the target-cell membrane, enabling cytotoxic killing through the release of death-inducing granules. These granules contain effector molecules such as granzymes, perforin, cathepsin C, and granulysin, which fuse with the target-cell membrane to initiate lysis [39]. An alternative mechanism involves the internalization of a granulysin-perforin-granzyme complex via endocytosis of the cytotoxic T-cell membrane by the target cell. Within the endosomal compartment, granulysin and perforin generate pores in the endosomal membrane, thereby allowing granzymes to escape into the cytoplasm and trigger apoptosis [40]. In addition to granule-mediated cytotoxicity, CD8+ T cells also employ the Fas-Fas ligand (FasL) pathway. FasL expressed on CD8+ T cells binds to Fas receptors on target cells, initiating signaling cascades through Fas-associated protein with death domains (FADD), which subsequently activate caspases and endonucleases, ultimately resulting in DNA fragmentation and programmed cell death [41].

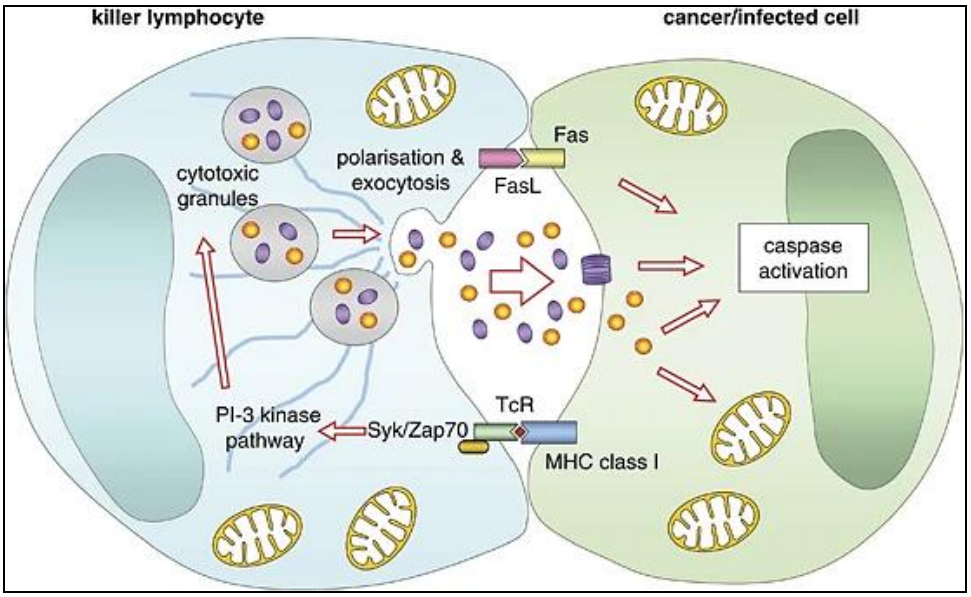

Fig 3: T-cell activation

2.1.2 Natural Killer (NK) cells

Innate immune responses play a crucial role in immunosurveillance, serving as the first line of defense against potentially harmful entities, including cancer cells. Natural Killer (NK) cells, a subset of innate immune cells, are particularly important in this context due to their ability to recognize and eliminate abnormal cells, such as those undergoing oncogenic transformation.

Natural killer cells and cytotoxic T lymphocytes (CTLs) function in a complementary manner to provide immune defense against viral infections and tumor development. CTLs exhibit antigen specificity, recognizing peptides derived from viral or tumor antigens that are presented by major histocompatibility complex (MHC) class I molecules [42, 43]. However, many tumors and virus-infected cells evade CTL-mediated killing by downregulating surface expression of MHC class I molecules [44, 45]. In contrast, NK cells are capable of detecting and eliminating such abnormal cells, as their activity is regulated through inhibitory receptors that normally recognize MHC class I. When these receptors engage with MHC class I molecules, NK cell activation is suppressed, but in the absence of this interaction, NK cells become activated and exert cytotoxic effects [47]. Moreover, NK cells can also respond to additional stress-induced signals, such as the expression of MHC class I chain-related (MIC) molecules, which are upregulated during viral infection or malignant transformation [48].

Natural killer cells contribute to tumor control through dual mechanisms: directly, by engaging and eliminating malignant cells, and indirectly, by modulating the function and activity of other immune populations within the tumor microenvironment.

Mature NK cells are morphologically identified as large granular lymphocytes containing cytotoxic granules that house perforin-a pore-forming protein-and granzymes, a family of serine proteases responsible for inducing apoptosis in target cells [49]. Upon engaging with a target, NK cells form an immunological synapse through which these granules are released by exocytosis, resulting in targeted cell lysis [50]. Beyond granule-mediated cytotoxicity, NK cells are also capable of eliminating tumor cells through death receptor pathways, including TRAIL and Fas ligand (FasL) signaling [51]. Moreover, NK cells utilize members of the tumor necrosis factor (TNF) superfamily to enhance their cytotoxic function. In addition to direct killing, activated NK cells secrete a wide range of cytokines and chemokines, many of which exert strong antitumor effects while simultaneously enhancing both innate and adaptive immune responses [52].

2.1.3 Macrophages

Macrophages, as key components of the innate immune system, are essential for maintaining tissue homeostasis, clearing apoptotic or excess cells, and orchestrating inflammatory responses against infections. Their role in cancer, however, is multifaceted-ranging from exerting antitumor effects during the initial stages of tumorigenesis to predominantly supporting tumor growth and progression in established malignancies [53]. A defining feature of macrophages is their remarkable plasticity, enabling them to adapt their functions in response to signals derived from the tumor microenvironment (TME). In many solid tumors-including breast, bladder, head and neck, glioma, melanoma, and prostate cancers-extensive macrophage infiltration is frequently associated with poor prognosis or enhanced tumor progression [54]. By contrast, in malignancies such as colorectal and gastric cancers, high macrophage density has been linked to improved clinical outcomes. These seemingly contradictory roles are attributed to macrophage plasticity, which generates heterogeneous phenotypes and functions depending on the cancer context [55].

3-Tumor Evasion from immune surveillance

During carcinogenesis, even though the immune system is capable of generating tumor-specific responses, the spontaneous eradication of tumors by immune mechanisms is a rare event. Clinical efforts to enhance these natural antitumor responses through immunotherapy have also shown limited success, largely due to the ability of cancer cells to employ multiple immune evasion strategies [56]. Such mechanisms include evading immune recognition and altering the activity of effector immune cells, frequently resulting in immunosuppression. This immunosuppressive

state not only diminishes effective immune surveillance but also promotes tumor progression and metastasis [56].

3.1 Major mechanisms of tumor escape from immune surveillance.

3.1.1 Avoidance of recognition of tumor cells by the host immune system.

Malignant tumor cells frequently exhibit low immunogenicity, primarily due to reduced or absent expression of major histocompatibility complex (MHC) molecules-most notably MHC class I-which impairs their recognition by cytotoxic T lymphocytes (CTLs) and prevents the initiation of apoptosis [57]. While tumor cells with diminished MHC I expression are, in principle, susceptible to natural killer (NK) cell activity, they often evade elimination because NK cells lack immunological memory and are typically too few in number relative to the expanding tumor population [57]. Conversely, many tumor cells maintain normal levels of MHC I expression, rendering them invisible to NK cells. At the same time, they escape CTL-mediated killing because they frequently fail to express tumor-associated antigens (TAA), thereby avoiding recognition and destruction [58].

3.1.2-The immunoregulatory effects of tumor cells on leukocyte functions.

Tumor cells release various substances known as tumor-derived soluble factors (TDSFs), including cytokines like interleukin 6 (IL-6), interleukin 10 (IL-10), tumor growth factor TGF-β, and vascular endothelial growth factor VEGF. These factors suppress the local immune response and can spread to lymphatic organs and blood vessels [59].

Tumors can shift the immune response balance from Th1 to Th2. Th1 responses are proinflammatory, led by interferon-γ (IFNγ), while Th2 responses produce anti-inflammatory cytokines such as interleukin 4 (IL-4) and interleukin 10 (IL-10). The anti-inflammatory Th2 response hinders the Th1-mediated antitumor inflammatory processes [60].

Neoplastic cells create an anti-inflammatory tumor environment by secreting chemokines attracting immunosuppressive regulatory T lymphocytes and Th2 lymphocytes. These cells counteract the antitumor immune response. Cytotoxic Tc lymphocytes, capable of killing tumor cells, lack receptors for these chemokines, hampering their directed action [61].

Cytokines and chemokines released by tumors also secrete soluble receptors inducing apoptosis of effector cells, like human leukocyte antigen 1 (HLA-1). Soluble receptors bind to surface structures of cytotoxic T lymphocytes and NK cells, blocking their receptors and preventing recognition of tumor cells, thereby decreasing effector cell activation.

Additionally, tumors deprive T cells of essential amino acids like tryptophan and arginine, impairing their function and proliferation. Amino acid metabolism changes and degradation, possibly mediated by myeloid-derived suppressor cells (MDSC), contribute to local and systemic immunosuppression. The enzyme indoleamine 2,3-dioxygenase (IDO) plays a role in reducing tryptophan locally, affecting immune responses [62].

3.1.3-Apoptosis of immunocompetent cells.

Certain tumors possess the ability to trigger apoptosis in immune effector cells. For example, melanoma cells release exosomes enriched with Fas ligand (FasL), which binds to Fas receptors on lymphocytes, initiating apoptosis. Exosomes, typically ranging from 80 to 200 nm in diameter, are small vesicles involved in intercellular communication, including the transmission of signals between antigen-presenting cells. Fas belongs to the death receptor family, which plays a central role in activating apoptotic signaling cascades in T lymphocytes [63]. During the early stages of tumor development, neoplastic cells secrete exosomes displaying FasL on their surface, inducing apoptosis of T cells either directly or indirectly, the latter occurring when dendritic cells internalize tumor-derived exosomes and subsequently mediate T-cell apoptosis [63]. Evidence also suggests that FasL is not exclusively released by tumor cells; activated NK cells can secrete FasL as well, thereby initiating their own apoptosis. This implies that each time an NK cell eliminates a tumor cell, it may simultaneously trigger its own death through Fas-FasL signaling [61].

3.1.4- Apoptosis evasion by tumor cells.

One of the essential conditions for maintaining physiological homeostasis is the efficient clearance of excess or damaged cells through apoptosis. However, tumor development is often accompanied by mutations that disrupt this process. For instance, the loss of pro-apoptotic regulators such as the tumor suppressor protein p53 and Bcl-2-associated X (Bax) protein, or the overexpression of anti-apoptotic proteins including B-cell lymphoma 2 (Bcl-2) and myeloid cell leukemia 1 (Mcl-1), can block the intrinsic apoptotic pathway, thereby allowing neoplastically transformed cells to escape elimination [64]. In addition, tumor cells secrete soluble phosphatidylserine (sP), which interferes with the clearance of apoptotic cells by binding to phosphatidylserine receptors (PSR) on dendritic cells and macrophages. This prevents recognition and phagocytosis of apoptotic cells and, instead, promotes the release of anti-inflammatory mediators such as IL-10, TGF-β, and prostaglandin E2 (PGE2) [65].

Furthermore, cytokines that normally exert antiproliferative and pro-apoptotic effects on healthy cells often become ineffective against tumor cells. This occurs as tumors progress, since many cancer cells exhibit reduced expression or structural modifications of cytokine receptors. A prominent example is TGF-β, which, due to alterations in the TGF-β type II receptor, may paradoxically stimulate tumor growth rather than suppress it. Similarly, IL-6 can inhibit melanoma proliferation during early tumorigenesis but later shifts to promoting tumor growth, advanced disease progression, and metastasis [66].

3.1.5-Immune checkpoints

Under normal physiological conditions, immunological pathways function appropriately to regulate immune responses against pathogens while preventing autoimmunity. These processes are tightly controlled by immune checkpoints, which act as regulatory mechanisms to balance activation and tolerance. However, in malignant settings, tumor cells can exploit these checkpoints to support their growth and survival. One of the most well-characterized checkpoints is programmed cell death protein 1 (PD-1), also referred to as cluster of differentiation 279 (CD279), a receptor expressed on the surface of T and B lymphocytes. PD-1 interacts with its two ligands, PD-L1 and PD-L2, to inhibit T-cell responses at the late effector stage, thereby limiting excessive immune activation.

Tumors frequently upregulate PD-L1 and PD-L2, enabling them to evade antitumor immunity [67]. Engagement of PD-1 with either PD-L1 or PD-L2 leads to persistent inhibition of T cells, inducing functional exhaustion and significantly weakening immune responses against cancer cells. Importantly, PD-L2 expression on tumor cells has been identified as a negative prognostic marker in several human malignancies [68]. Therapeutically, blockade of PD-1 or PD-L1 with monoclonal antibodies has demonstrated the ability to restore antitumor immunity, offering an effective strategy to enhance immune-mediated tumor control [69].

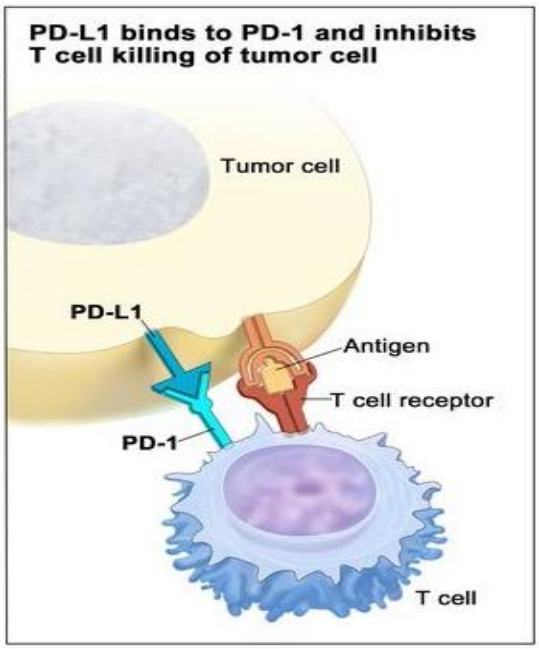

Fig 4: Ligands of PD-1

Another immune checkpoint frequently exploited by tumors to suppress antitumor immunity is cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), also referred to as cluster of differentiation 152 (CD152). CTLA-4 plays a critical role during the early phases of the immune response by competing with CD28 for binding to B7 ligands on antigen-presenting cells (APCs). This competition prevents full T-cell activation and effectively shortens the duration of T-cell activity [68]. Tumor cells often constitutively express CTLA-4, where it functions as a negative regulator of T-cell proliferation and effector activity, thereby contributing to immune evasion [70].

In addition, tumors can escape immune surveillance through the lymphocyte activation gene 3 (LAG-3) pathway, another inhibitory checkpoint receptor expressed on multiple immune cell types, including activated T cells, NK cells, B cells, and plasmacytoid dendritic cells. LAG-3 downregulates immune function by impairing cellular proliferation, activation, and homeostasis in a manner analogous to CTLA-4 and PD-1 [71]. Given its role in immune suppression, LAG-3 has become a major target of drug development programs, and numerous clinical trials are investigating novel therapies designed to inhibit this checkpoint and restore antitumor immunity.

4. Immunotherapeutic Approaches

Traditional cancer treatments such as surgery, chemotherapy, and radiation therapy have been the mainstay in cancer management. However, these approaches often exhibit limitations in terms of specificity, efficacy, and side effects. Immunotherapy represents a paradigm shift by empowering the body's immune system to recognize and eliminate cancer cells selectively.

4.1 Types of Immunotherapies

4.1.1 Immune checkpoint inhibitors (ICIs)

The immune system plays a pivotal role in recognizing and eliminating abnormal cells, including cancer cells. Immune checkpoints act as regulatory switches that can be hijacked by tumors to evade immune surveillance. ICIs, by disrupting these checkpoints, aim to unleash the immune system's full potential in combating cancer.

4.1.1.1 Blockade of CTLA-4

CTLA-4 inhibitors, such as ipilimumab, block inhibitory signals, enhancing T cell activation and proliferation. Ipilimumab, a fully human IgG1 monoclonal antibody, functions by blocking CTLA-4 activity and was the first checkpoint inhibitor to receive approval, initially recommended in 2011 for the treatment of melanoma [72]. Since then, its therapeutic application has expanded to include advanced renal cell carcinoma and metastatic colorectal cancer. More recently, in 2020, the U.S. Food and Drug Administration (FDA) approved the combination of nivolumab (Opdivo) with ipilimumab, administered intravenously, as a first-line treatment option for adult patients diagnosed with malignant pleural mesothelioma (MPM), highlighting its broader clinical utility [73].

4.1.1.2 PD-1/PD-L1 Pathway Blockade

Inhibitors targeting the PD-1/PD-L1 pathway, including nivolumab and pembrolizumab, disrupt the suppression of T cell activity, promoting an anti-tumor immune response.

Nivolumab, a fully human immunoglobulin G4 (IgG4) monoclonal antibody, selectively suppresses PD-1 activity by blocking the interaction between PD-1 receptor and its ligands (PD-L1 and PD-L2). Approved by the FDA in 2014 and 2015 for melanoma and renal cell carcinoma, respectively, Nivolumab has demonstrated clinical activity in various tumor types [74].

Pembrolizumab, another humanized IgG4 monoclonal antibody, disrupts the PD-1/PD-L1 pathway and has received FDA approval for treating multiple tumor types based on robust responses and a favorable safety profile [75]. The FDA recently confirmed (13 October 2021) that a combination of pembrolizumab and chemotherapy drugs, with or without bevacizumab, can have therapeutic benefits for patients with recurrent metastatic cervical cancer whose tumour cells express high levels of PD-L1 [76].

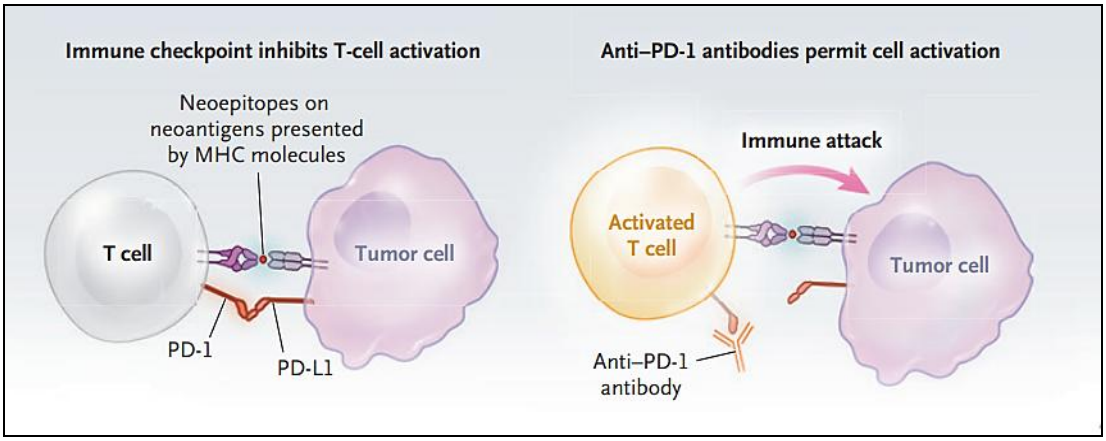

Fig 5: Mechanism of PD1/PDL1 and CTLA-4 blockade.

4.1.2 Cancer vaccine

Immunotherapy vaccines operate through various mechanisms to enhance the immune system's ability to recognize and attack cancer cells. Antigen-presenting cells (APCs) play a crucial role in presenting tumor-specific antigens to T cells, thereby initiating a specific immune response.

Cancer vaccines aim to stimulate the immune system to mount targeted responses against malignant cells by inducing tumor-specific or tumor-reactive immunity in vivo. Among the various approaches, peptide-based vaccines remain the most widely studied; these vaccines are composed of immunogenic epitopes derived from tumor-associated or tumor-specific antigens and are typically administered alongside adjuvants to enhance immunogenicity. Dendritic cells (DCs) serve as natural adjuvants due to their pivotal role in initiating and sustaining immune responses. DC-based vaccination can be achieved either by directly delivering antigens to DC receptors in vivo or by generating antigen-loaded DCs ex vivo and reintroducing them into patients. DNA vaccines represent another strategy, wherein plasmids encoding tumor antigens are delivered to the patient, leading to in situ expression of these antigens and subsequent activation of tumor-specific T-cell responses [77, 78].

Therapeutic cancer vaccines are designed as active immunotherapies, particularly for advanced disease, with the goal of generating durable antitumor T-cell responses by immunizing patients against tumor-associated or tumor-specific antigens. Despite decades of investigation, only one therapeutic DC-based vaccine-Sipuleucel-T (Provenge™)-has received FDA approval, in 2010, for the treatment of metastatic castration-resistant prostate cancer. Nonetheless, the development of effective, safe, and durable therapeutic cancer vaccines remains a significant challenge in oncology. These efforts, however, have provided critical insights that form the foundation for other immunotherapeutic modalities, including monoclonal antibody therapies, which are now central to cancer treatment [79].

4.1.3 Adoptive cell immunotherapy (ACT)

Adoptive cell therapy (ACT) represents an advanced form of immunotherapy in which immune cells, most commonly T lymphocytes, are isolated from the patient, expanded or genetically modified ex vivo, and subsequently reinfused into the patient to enhance the immune system's ability to eliminate disease, with particular emphasis on cancer treatment. The primary focus of cellular adoptive therapy is on T cell therapies, including chimeric antigen receptors CAR-T therapy, CAR-NK therapy, macrophage-based immunotherapy, and dendritic cell therapy [80].

CAR T-cell therapy, a specific form of cellular immunotherapy, entails the laboratory engineering of T cells to enhance their cancer-targeting capabilities. The first FDA-approved CAR T cell therapy, tisagenlecleucel (Kymriah), was sanctioned in 2017 for the treatment of pediatric and young adult Acute Lymphoblastic Leukemia. Subsequently, six CAR T-cell therapies have gained FDA approval, all for the treatment of blood cancers [81].

In CAR T-cell therapy, T cells are collected from the patient's blood, genetically modified in the laboratory to express chimeric antigen receptors (CARs) recognizing specific proteins on cancer cells, and then expanded in the laboratory before being reintroduced into the patient's bloodstream. This process has shown effectiveness against various forms of aggressive, relapsed, or refractory non-Hodgkin lymphoma [83-84].

5. Conclusion

In conclusion, a comprehensive understanding of the strategies employed by tumor cells to evade immune surveillance is paramount for the development of effective immunotherapeutic interventions. This review synthesizes existing knowledge on the subject, shedding light on the intricate mechanisms that contribute to immune escape. By delineating these evasion strategies, Ultimately, unraveling the complexities of immune evasion in the tumor microenvironment will pave the way for the development of more targeted immunotherapeutic approaches.

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