Razi Med J. 2025;1(4):405-415
https://doi.org/10.69667/rmj.25417
Razi Medical Journal
https://razi.edu.ly/rmj/index.php/hm

Review article

Understanding the Hidden Immune Evasion Mechanisms by Cancer Cells and Therapeutic Approaches

Marwah Rasah[1], J. M. Jbireal* [2,3]

[1]*Department of Zoology, Faculty of Arts and Sciences, Gharyan University, Libya.*
[2]*Department of Physiology, Faculty of Medicine, Sabratha University, Libya.*
[3]*Knowledge Center for Scientific Consultation, Academic Services, and Research, Sabratha, Libya.*
***Corresponding author.** j.jbireal@yahoo.de*

Abstract
The immune system plays a fundamental role in recognizing and eliminating malignant cells to maintain cellular homeostasis. However, the tumor microenvironment (TME), composed of tumor and stromal cells, extracellular matrix, vascular components, and soluble mediators, promotes cancer progression by enabling immune escape mechanisms. Advances in cancer immunology have led to the development of various immunotherapeutic strategies designed to restore antitumor immune responses. These include monoclonal antibodies that selectively target tumor-associated antigens, therapeutic cancer vaccines that stimulate durable immune protection, and adoptive cell therapies that enhance tumor-specific T-cell activity. Although these approaches have shown significant clinical benefits, immune suppression within the TME continues to limit treatment efficacy. A deeper understanding of immune checkpoint pathways and tumor-induced immune dysfunction is therefore essential to improve current therapies and guide future innovations in cancer management.
Keywords. *Cancer Immunotherapy, Immune Escape, Tumor Microenvironment, Cancer Vaccines, Adoptive T-cell Therapy.*

***Received**: 05/10/25*
***Accepted**: 06/12/25*
***Published**: 15/12/25*

Introduction

The human immune system is a harmonious collection of mechanisms that work together to shield people against illness. Tumor cells and invasive pathogens, such as bacteria and viruses, are effectively identified and eliminated without harming healthy cells. Additionally, immune cells are essential for preventing the emergence and growth of malignancies since they are a basic part of stromal cells. Conversely, the intricate ecosystem known as the tumor microenvironment (TME) promotes the growth and survival of tumor cells. The majority of the TME is made up of tumor cells, stromal cells, extracellular matrix, peripheral blood arteries, and the secretory products of different cells, including cytokines and cellular metabolites [1].

Therefore, one of the biggest problems facing modern medicine is cancer [2]. The immune system is necessary for identifying and eliminating aberrant cells, preserving cellular homeostasis, and guarding against cancerous alterations [3]. Nevertheless, cancer cells employ several intricate strategies to avoid immune surveillance, which allows them to proliferate uncontrollably and eventually develop into potentially fatal tumors [4, 5]. Accordingly, immune evasion pathways are revealed by recent advancements in immunology and oncology, offering fresh perspectives on how cancer cells evade immune responses [6-8].

Cancer microenvironment and immune cells (TME)

Cancer cells, immune cells, blood arteries, fibroblasts, signaling molecules, and the extracellular matrix (ECM) make up the complex, diverse, and dynamic tumor microenvironment [9]. The main source of energy for cells is the oxidative breakdown of glucose. Even in oxygen-sufficient environments, tumor cells prefer to use glycolysis to turn glucose into lactate, while normal cells obtain energy by completely oxidizing glucose to CO2 and water in aerobic conditions. The Warburg effect is the term used to describe this [10]. Additionally, the ECM, immune cells, stromal cells, and soluble substances are all components of the TME that work together to promote the survival, growth, and spread of cancer cells [11, 12]. On the other hand, creating successful treatment plans requires an understanding of the TME's molecular mechanisms and how they affect metastasis. Through a variety of ways, the TME actively influences the course of cancer rather than acting as a passive environment for tumor formation. For instance, fibroblasts and other stromal cells can develop into cancer-associated fibroblasts (CAFs) [13]. Depending on their level of activity and the signals they receive

Razi Med J. 2025;1(4):405-415
https://doi.org/10.69667/rmj.25417
Razi Medical Journal
https://razi.edu.ly/rmj/index.php/hm

from the tumor and its surroundings, immune cells inside the TME, such as neutrophils, T cells, and macrophages, can either repress or encourage tumor growth and metastasis [14].

Furthermore, in tumor cells, both aerobic glycolysis and glutamine catabolism create high amounts of lactate, rendering the TME acidic [15]. Although most cancer-metabolism-related investigations have considered Lactate as a metabolic waste product in the Warburg effect, recent studies have suggested that lactate is a possible fuel [16]. Macrophages are among the immune cells in the TME that are crucial for tumor metastasis, in addition to other immune cell types (Figure 1). When these cancer cells are getting ready to spread to other bodily tissues, macrophages in the main tumor first aid in the growth of the tumor. The resident macrophages in the distal tissues form a hospitable environment called a pre-metastatic niche upon receiving signaling instructions created by primary tumor-derived extracellular vesicles that could modify the activity of these macrophages. After settling in these organs, cancer cells eventually attract immune cells like monocytes, which develop into tumor-associated macrophages and aid in the spread of the tumor. Thus, in primary tumors, macrophages aid in tumor cell proliferation and prepare metastatic sites for the dissemination and creation of new tumors [17]. Although immune cells normally protect against diseases within the TME, they can be altered to aid tumor growth. Tumor-associated macrophages (TAMs) support tumors by reducing immunological responses and promoting angiogenesis, the process of creating new blood vessels [18]. Furthermore, by activating immunological checkpoints to suppress the immune response, tumor cells can evade immune attack [19]. A tumor is surrounded by a TME, which is made up of different cell types that communicate with one another. The components of TME are stromal, immunological, and cancer cells, as well as extracellular matrix components (Figure 1) [20].

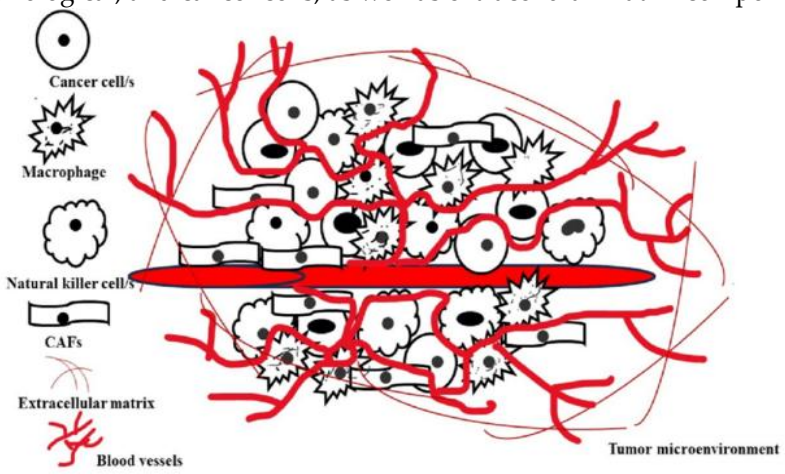

Figure 1. Cells of the tumor microenvironment (TME).

This immune cell location, makeup, and state of activation influence the course of cancer and adjust the response to treatment. Quick developments in spatial transcriptomics and proteomics profiling allow understanding the heterogeneous immune solid tumor landscape while maintaining geographic details about the cellular Tumor, immunological, and stromal cell architecture and functional phenotype [21, 22]. This high-resolution information of TME enables clinicians to develop specific treatments based on customized immunological profiles [8]. Macrophages, neutrophils, natural killer (NK) cells, dendritic cells (DCs), bone marrow-derived suppressor cells (MSDCs), and tumor-infiltrating lymphocytes (TILs) make up the immunological landscape in the TME (Figure 1). These cell types differentially interact with the molecular and cellular elements of TME engineering, either tumor development or repression, depending on their activation status and interaction [8].

Mechanisms of immune evasion in cancer

Tumor-induced immune suppression

Tumor cells employ a variety of strategies to avoid the immune system. One significant mechanism is tumor-induced immune suppression [23, 24]. This includes creating an immunosuppressive microenvironment that impedes the expansion and function of immune cells, facilitating unregulated growth and persistence of malignant cells [25]. Specifically, tumors can disrupt the immune system by secreting immunosuppressive compounds, enlisting regulatory immune cells, as well as generating checkpoint molecules that hinder immunological responses. Usually, the immune system recognizes and gets rid of malignant cells [26, 27]. Cellular and soluble components typically make up this

Razi Med J. 2025;1(4):405-415
https://doi.org/10.69667/rmj.25417
Razi Medical Journal
https://razi.edu.ly/rmj/index.php/hm

immunosuppressive milieu, which encourages tumor growth and helps malignancies evade the immune system [28, 29]. The primary cellular components of the tumor microenvironment (TME) are innate immune cells like myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), tumor-associated dendritic cells (tDCs), and adoptive immune cells like regulatory T cells (Tregs). Additionally, it has been demonstrated that this process involves small molecules, including vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), and cytokines like interleukin-10 (IL-10) generated by immunosuppressive or cancer cells [30-32].

MDSCs are immature myeloid cells deriving from hematopoietic stem cells residing in the bone marrow. The precursor of MDSCs migrates out of the bone marrow and travels into the extramedullary sites, induced by factors, and becomes an MDSCs [33, 34]. Following their appearance in the TME, MDSCs altered how immune cells and cancer cells interacted, which led to immunosuppression [35]. Additionally, the epithelial–mesenchymal transition (EMT) transcriptional factors, including Snail and Twist1, engaged the immunosuppressive cells, such as MDSCs, and promoted the expression of immunosuppressive checkpoints, resulting in the immunosuppressive TME. Immunosuppressive substances then enabled tumor cells to undergo EMT, which enhanced the progression of the tumor [36]. One of the primary methods by which tumors cause immune suppression is the creation of soluble chemicals that inhibit immune cell activation. Tumor cells, for instance, often release high concentrations of cytokines, such as transforming growth factor-beta (TGF-β) [37], interleukin-10 (IL-10) [38], and VEGF [39, 40], all of which contribute to an immunosuppressive environment. Notably, TGF-β is a potent immunosuppressive cytokine that inhibits the activation and development of T cells [41, 42] and natural killer (NK) cells [43, 44], both crucial for anti-tumor immunity.

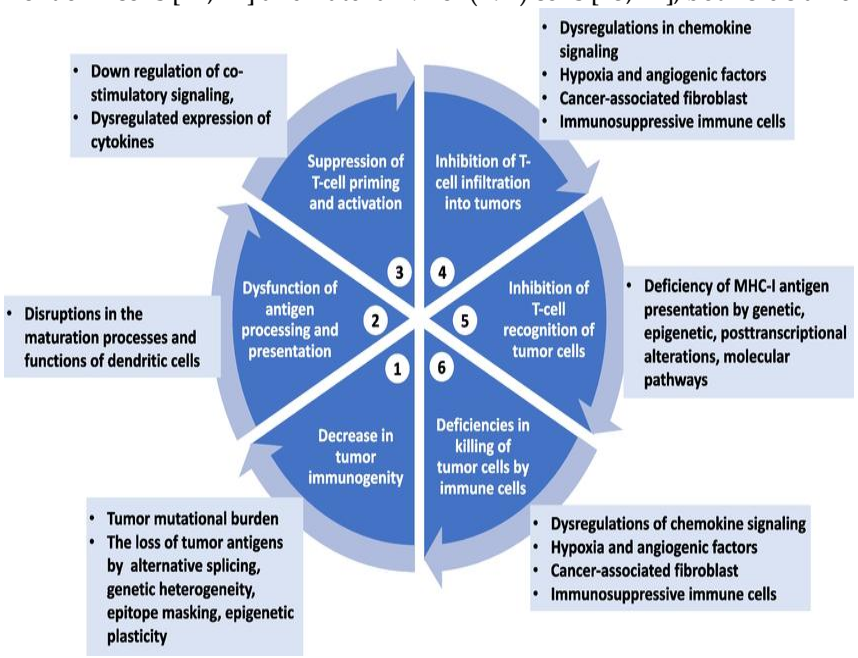

Figure 2. Mechanism of immunological evasion in the cancer immune cycle [45].

Antigen presentation and recognition

Tumor cells have the potential to reduce antigen presentation, which makes them less noticeable and hinders immune cells, especially T cells, from recognizing and interacting with tumor-specific antigens [46] (Figure 1). Numerous mechanisms can be attributed to these phenomena. Firstly, tumor cells can promote the deletion or acquisition of mutations in major histocompatibility complex (MHC) genes, resulting in diminished or missing production of MHC molecules [47-50]. Secondly, there may be disruptions in the loading of tumor antigens onto MHC molecules. These disruptions can include changes in immunoproteasome activity (leading to peptide deficiency), disruption of peptide getting into the endoplasmic reticulum via transporter linked to antigen processing (TAP), and disruptions involving chaperone proteins [46, 51]. Furthermore, both mutational and non-mutational changes supply cancer cells with a distinctive antigenic landscape in contrast to their normal equivalents, at least theoretically boosting the availability of CD8+ CTLs [52, 53]. However, malignant cells frequently lack the molecular machinery necessary for the correct

Razi Med J. 2025;1(4):405-415
https://doi.org/10.69667/rmj.25417
Razi Medical Journal
https://razi.edu.ly/rmj/index.php/hm

processing and expression of such novel antigens on the cell surface, which enables them to evade immune identification [52].

Defects in the antigen processing and presentation (APP) machinery can be acquired by neoplastic cells through genetic mechanisms [54], such as loss of heterozygosity (LOH) at chromosome 6p, which includes the MHC locus, as reported in individuals with non-small cell pulmonary carcinoma (NSCPC) and homologous recombination- insufficient (HRD) high-grade serous ovarian cancer (HGSOC) [55–57].

On the other hand, current research has shown that one mechanism underlying the immune escape is the tumor-intrinsic factor YTHDF1, a m6A reader that modulates the translation of critical lysosomal genes. YTHDF1 deficiency has been found to restore the proteolysis of MHC-I molecules and their related antigens, hence boosting tumor immune surveillance. This process not only promotes immune evasion but also facilitates opposition immunological ICIs, as YTHDF1 deficiency helps to turn "cold" tumors into "hot" tumors to improve their susceptibility to immunotherapy [58].

Moreover, MHC class I and MHC class II expression play crucial roles in establishing resistance to immunotherapy, albeit through separate methods. In malignancies with faulty IFN-γ signaling, decreased MHC-I expression hampers T cell identification, leading to immune evasion. However, cancers that maintain high MHC-I levels may still respond to immunotherapy, suggesting that techniques targeting the NF-κB pathway to sustain MHC-I expression could overcome resistance [59, 60].

These results thus demonstrate the significance of MHC molecules in immune response modulation and offer possible therapeutic approaches for combating immune checkpoint inhibitor resistance. Many mechanisms support immune evasion in acute myeloid leukemia (AML) (Figure 3) [61, 62].

The precise role of each mechanism in the development of leukemia immunological tolerance, their activity in the secondary cancer site (peripheral blood) compared to bone marrow (the original cancer site), and the effects of AML therapy and genetics on them deserve further study. In AML, leukemic blasts interact with the bone marrow microenvironment to create an immunosuppressive niche. Key features include reduced antigen presentation by dendritic cells and impaired cytotoxic activity of natural killer (NK) cells and T lymphocytes. Leukemic cells often overexpress immune checkpoint molecules (such as PD-L1), which inhibit T-cell activation and promote immune escape. Additionally, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) are expanded, further dampening anti-tumor immune responses [61].

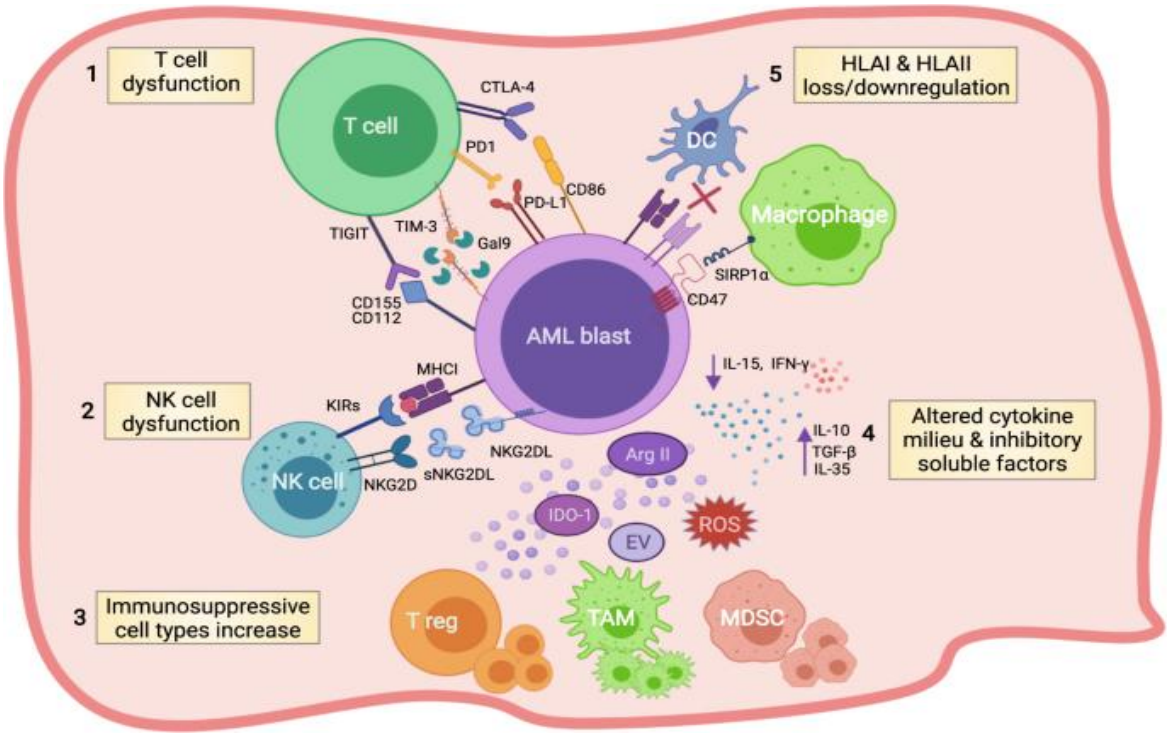

Figure 3. The dysfunctional immune landscape associated with acute myeloid leukemia.

Razi Med J. 2025;1(4):405-415
https://doi.org/10.69667/rmj.25417
Razi Medical Journal
https://razi.edu.ly/rmj/index.php/hm

Furthermore, in several donor transplant situations, the downregulation of HLA class II molecules via epigenetic processes has been noted [63, 64]. Leukemia antigen presentation by immature antigen-presenting cells or splenic CD8α+ dendritic cells has been demonstrated in mouse models to generate T-cell tolerance, particularly CD8+ and deletional T-cell tolerance [65].

Tumor TME modulation

Cancer cells, stromal cells, immune cells, and signaling molecules make up the intricate ecosystem that is the TME [66]. This microenvironment plays a vital role in tumor formation, metastasis, and immune evasion. Through a variety of mechanisms that together encourage immune suppression and enable tumor cells to evade immune surveillance, the TME actively influences the immune response rather than acting as a passive environment for tumor growth [67]. Additionally, all cancer cells demonstrate a major metabolic rewiring as contrasted to their normal counterparts [68]. While for long such metabolic abnormalities were understood as a pure consequence of the accumulating trophic needs of malignant cells, it is now clear that certain metabolic pathways that are changed in cancer actively induce immunosuppression [69].

In the presence of serum antibody, certain tumor-specific antigens have been observed to disappear from the surface of cancerous cells. Such "antigen loss variants" are generally discovered in fast-dividing malignancies [70]. Due to the increased mitotic rate of cancer cells and their genomic instability, these antigen-loss variants emerge. If these antigens are not needed for the proliferation or survival of the altered phenotype, these antigen-loss mutations have a growth edge in the host, allowing them to endure and proliferate [71]. Being the most prevalent malignancy in women, breast cancer (BC) is one of the most researched tumors at all levels [72].

By eliminating immunomodulatory neoplastic cells, immune cells that have infiltrated the tumors stop them from growing. However, by affecting tumor immunogenicity and choosing tumor clones that can induce immune fatigue, they may also be responsible for the development of tumor resistance to treatment [73]. Moreover, the immune cells in the TME have an important role in cancer development and metastasis. The type 1 helper T cells (Th1), cytotoxic T lymphocytes (CTLs), and natural killer cells (NK cells) are connected with an immunological stimulant microenvironment. Conversely, the regulatory cells of the TME, particularly type 2 helper T cells (Th2), TAMs, regulatory T cells (Tregs), and myeloid-derived suppressor cells (MDSCs), have a connection with immunosuppressive microenvironment and adverse effects [74, 75]. These cells limit tumor growth by eliminating immunogenic neoplastic cells or modifying cancer immunogenicity, enabling tumor evacuation [76].

Furthermore, immunological evasion depends on metabolic reprogramming within the TME [77, 78]. Tumor cells usually shift towards glycolysis, even under normoxic conditions [79, 80]. By supplying biosynthetic precursors, this enables them to multiply quickly [81]. As a result of this metabolic reprogramming, tumor cells compete with infiltrating immune cells for essential resources, including glucose and glutamine [82, 83]. This nutritional deficit in the TME affects the function and development of effector T cells [83, 84].

Immune checkpoint inhibition

Although uncontrolled development is clearly a common biological property of all tumors, the key pathophysiologic characteristics of cancer responsible for morbidity and mortality are the ability to penetrate beyond natural tissue barriers and to metastasize. Both of these traits are linked to a significant disruption of tissue architecture and are never observed in normal tissues or benign tumors [85]. Moreover, immunosuppression results from the interaction of PD1 expressed in T cells with PD-L1 on cancer cells, which inhibits T cell survival and proliferation. Pembrolizumab and nivolumab are ICIs that target PD1 to inhibit PD1/PD-L1 interaction [86]. On the other hand, durvalumab and atezolizumab work against PD-L1 to prevent it from interacting with PD1 [87, 88].

Razi Med J. 2025;1(4):405-415
https://doi.org/10.69667/rmj.25417
Razi Medical Journal
https://razi.edu.ly/rmj/index.php/hm

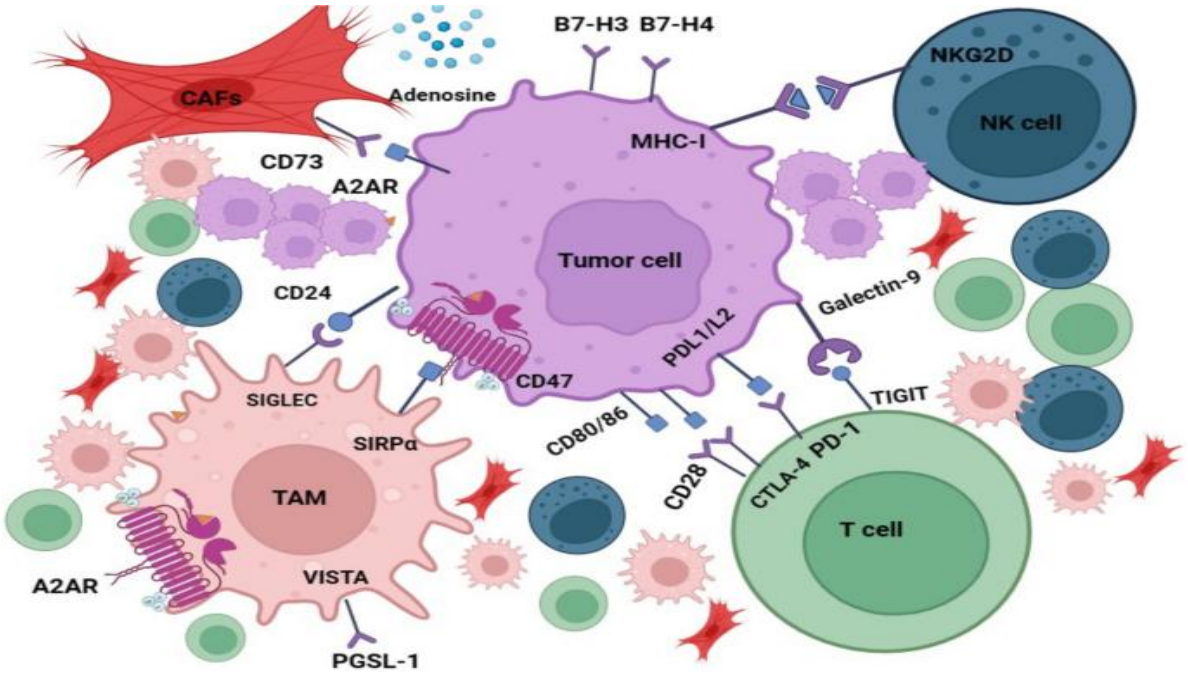

Figure 4. Multiple immunologic checkpoints in the tumor microenvironment [89].

This figure demonstrates the intricate network of immune checkpoint pathways that modulate antitumor immunity within the tumor microenvironment. Tumor cells and immunosuppressive cell subsets, including regulatory T cells and myeloid-derived suppressor cells, express inhibitory ligands such as PD-L1, CD80/CD86, and ligands for TIM-3 and LAG-3. Engagement of these ligands with their receptors on activated T cells attenuates T-cell proliferation, effector function, and cytokine secretion, thereby facilitating immune escape. The figure underscores the redundancy and cooperation among checkpoint pathways, providing a mechanistic rationale for therapeutic strategies targeting multiple checkpoints to achieve more robust and sustained antitumor responses.

PD-L1 and PD-L2 are ligands for the PD-1 receptor, with PD-L1 being expressed on both cancer and immune cells. One important biomarker for predicting how some tumors may react to anti-PD-1/PD-L1 treatments is PD-L1. By binding to PD-1 and CD80, PD-L1 inhibits T-cell activation, limiting T-cell trafficking and proliferation, which inhibits cancer cell killing [90, 91]. Additionally, CTLA-4, a protein from the immunoglobulin superfamily, is expressed exclusively on activated T cells and regulates early T-cell activation. It suppresses the co-stimulatory receptor CD28, although both bind to the same B7 ligand on B cells and antigen-presenting cells (APCs). CTLA-4 is elevated 24 hours after T-cell activation and peaks 2-3 days later, whereas CD28 is expressed on naïve T cells. CTLA-4 serves a vital function in inhibiting T-cell responses; without it, T-cell proliferation becomes uncontrolled. This discovery motivated researchers to study whether blocking CTLA-4 could improve anti-tumor immune responses [92, 93].

Another crucial factor, the T cell immunoreceptor with Ig and ITIM domains (TIGIT), is potentially developing into an immunological checkpoint. T cells, NK cells, and other immune cells, such as dendritic cells and regulatory T cells, express this inhibitory receptor. It operates as a crucial immunological checkpoint, especially within the TME. TIGIT and CD226 (DNAM-1) compete to bind to CD112 and CD155, two shared ligands. When TIGIT binds to CD155, it conveys an inhibitory signal via the immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. This reduces T cell activation, proliferation, cytokine generation, and the killing potential of T cells and NK cells. As a result, TIGIT leads to immune evasion by cancer cells [94, 95].

Approaches for cancer immunotherapy

According to the hypothesis of cancer immunoediting, the immune system can paradoxically either stimulate or prevent the development of tumor tissue. This process is controlled by a complicated mechanism that consists of three primary stages: elimination, equilibrium, and escape [96]. The concept of immunotherapy dates back to 1796, when Edward Jenner successfully used cowpox inoculation to prevent smallpox [97]. In 1997, the U.S. Food and Drug Administration (FDA) approved the first antibody-based cancer therapy, Rituximab, for follicular lymphoma, marking the beginning of monoclonal antibody therapy in oncology. Over the next decade, several more antibodies gained approval, including Trastuzumab (1998), Gemtuzumab ozogamicin (2000), Alemtuzumab (2001), Ibritumomab tiuxetan (2002),

Razi Med J. 2025;1(4):405-415
https://doi.org/10.69667/rmj.25417
Razi Medical Journal
https://razi.edu.ly/rmj/index.php/hm

Tositumomab (2003), Cetuximab (2004), Bevacizumab (2004), Panitumumab (2006), Ofatumumab (2009), Ipilimumab (2011), and Brentuximab vedotin (2011) [98]. Additionally, the creation of cancer vaccines followed the success of monoclonal antibodies. The application of immunologic knowledge into therapeutic vaccines is demonstrated by the 2010 approval of Sipuleucel T, the first cell-based cancer vaccine, for prostate cancer [97].

These vaccines can be composed of many materials, including TAAs, entire tumor cells, or DCs, all designed to initiate a powerful immune response, particularly targeting cancer cells. The fundamental method of cancer vaccines is presenting tumor antigens to the immune system. These antigens, which can be proteins, peptides, or other compounds, are either specific to cancer cells or overexpressed in them. Upon administration, cancer vaccines expose these antigens to APCs, which process and display them on their surface with large MHC molecules [99].In order to activate CTLs, which subsequently seek out and eliminate tumor cells expressing the same antigens, this antigen presentation is essential [99, 100].

In contemporary cancer immunotherapy, three major strategies are recognized: Use of specific antibodies (monoclonal antibodies) directed against tumor-associated antigens, therapeutic vaccination, using proteins, peptides, or tumor-associated antigens to elicit an adaptive immune response and adoptive T cell transfer therapies: reinfusing immune cells (e.g., cytotoxic T lymphocytes or dendritic cells), often expanded or modified ex vivo, to target and destroy tumor cells [101]. On the other hand, based on the preliminary results of a series of experimental studies and the actual scenario observed in clinical studies, it can be determined that trogocytosis is an important mechanism to block CAR-T/NK cell therapy, and blocking trogocytosis can further release the therapeutic potential of CAR-T/NK. Currently, a number of strategies have been put out to address the short-term medication resistance and CAR-T/NK cell malfunction brought on by trogocytosis [102].

Conclusion

One of the biggest challenges in oncology is the intricate and varied mechanisms of immune evasion in cancer, which call for a thorough comprehension of the underlying molecular processes. The concept of individualized cancer immunotherapy has received substantial popularity in recent years. The lack of standardized assessment techniques for the majority of parameters and the insufficient knowledge of cancer-immune interaction parameters are two of the main obstacles to accomplishing this ambitious goal. As TME is a potential target, it is vital to discover TME biomarkers, which can be immunological biomarkers like PDL-1, angiogenic biomarkers like VEGF and HIF-1, cancer-associated fibroblasts (CAFs), and stromal cells. Cancers evade immune surveillance primarily through tumor-induced immune suppression, immunological checkpoint regulation, and TME modulation. Therefore, determining the nature of these immunosuppressive cells in the TME of advanced cancers by individual analysis is essential for creating relevant treatments. In addition, the production, expansion, recruitment, and activation of immunosuppressive cells in the tumor microenvironment entail complicated mechanisms, making it challenging for a single strategy to target any one of these cells to generate substantial anti-tumor effects. However, the additional mechanisms of these cells participating in the tumor immune response and the optimization of clinical use of medicines targeting these cells are needed.

Funding

The authors reported no funding received for this study.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

The authors acknowledge the Knowledge Center for Scientific Consultation, Academic Services, and Research (Sabratha, Libya) for support with the scientific review of this work.

References

1. Hui L, Chen Y. Tumor microenvironment: sanctuary of the devil. Cancer Lett. 2015;368(1):7-13.
2. Caner A. Immune escape mechanism of cancer. Curr Mol Biol Rep. 2024;10:9-19.
3. Li Y, Liu XL, Zhang X, Pan W, Tang B. Immune cycle-based strategies for cancer immunotherapy. Adv Funct Mater. 2021;31(46):2107540.

4. Dutta S, Ganguly A, Chatterjee K, Spada S, Mukherjee S. Targets of Immune Escape Mechanisms in Cancer: Basis for Development and Evolution of Cancer Immune Checkpoint Inhibitors. Biology (Basel). 2023 Jan 30;12(2):218.
5. Messerschmidt JL, Prendergast GC, Messerschmidt GL. How cancers escape immune destruction and mechanisms of action for the new significantly active immune therapies: helping nonimmunologists decipher recent advances. Oncologist. 2016;21(2):233-43.
6. Xu X, Chen J, Li W, Feng C, Liu Q, Gao W, He M. Immunology and immunotherapy in gastric cancer. Clin Exp Med. 2023 Nov;23(7):3189-204.
7. Greten TF, Schwabe R, Bardeesy N, Ma L, Goyal L, Kelley RK, Wang XW. Immunology and immunotherapy of cholangiocarcinoma. Nat Rev Gastroenterol Hepatol. 2023 Jun;20(6):349-65.
8. Mundhara N, Sadhukhan P. Cracking the Codes behind Cancer Cells' Immune Evasion. Int J Mol Sci. 2024 Aug 15;25(16):8899.
9. Norton KA, Gong C, Jamalian S, Popel AS. Multiscale Agent-Based and Hybrid Modeling of the Tumor Immune Microenvironment. Processes (Basel). 2019 Jan;7(1):37.
10. Chen L, Wang Y, Hu Q, Liu Y, Qi X, Tang Z, et al. Unveiling tumor immune evasion mechanisms: abnormal expression of transporters on immune cells in the tumor microenvironment. Front Immunol. 2023;14:1225948.
11. Tiwari A, Trivedi R, Lin SY. Tumor microenvironment: barrier or opportunity towards effective cancer therapy. J Biomed Sci. 2022;29(1):83.
12. Shen M, Kang Y. Complex interplay between tumor microenvironment and cancer therapy. Front Med. 2018;12(4):426-39.
13. Baghban R, Roshangar L, Jahanban-Esfahlan R, Seidi K, Ebrahimi-Kalan A, Jaymand M, et al. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Commun Signal. 2020;18(1):59.
14. Ramos RN, Amano MT, Paes Leme AF, Fox JW, de Oliveira AK. Editorial: tumor microenvironment (TME) and tumor immune microenvironment (TIME): new perspectives for prognosis and therapy. Front Cell Dev Biol. 2022;10:971275.
15. Wise DR, DeBerardinis RJ, Mancuso A, Sayed N, Zhang XY, Pfeiffer HK, et al. Myc regulates a transcriptional program that stimulates mitochondrial glutaminolysis and leads to glutamine addiction. Proc Natl Acad Sci U S A. 2008;105(48):18782-7.
16. Faubert B, Li KY, Cai L, Hensley CT, Kim J, Zacharias LG, et al. Lactate metabolism in human lung tumors. Cell. 2017;171(2):358-71.e9.
17. Bied M, Ho WW, Ginhoux F, Blériot C. Roles of macrophages in tumor development: a spatiotemporal perspective. Cell Mol Immunol. 2023;20(9):983-92.
18. Lu C, Liu Y, Ali NM, Zhang B, Cui X. The role of innate immune cells in the tumor microenvironment and research progress in anti-tumor therapy. Front Immunol. 2022;13:1039260.
19. Wang Y, Zhang H, Liu C, Wang Z, Wu W, Zhang N, et al. Immune checkpoint modulators in cancer immunotherapy: recent advances and emerging concepts. J Hematol Oncol. 2022;15(1):111.
20. Fathah D, Ejaz S. Role of tumor microenvironment in cancer promotion, development of drug resistance and cancer treatment. J Egypt Natl Canc Inst. 2025;37(1):59.
21. DiMauro F, Arbore G. Spatial Dissection of the Immune Landscape of Solid Tumors to Advance Precision Medicine. Cancer Immunol Res. 2024;12(7):800-13.
22. Seferbekova Z, Lomakin A, Yates LR, Gerstung M. Spatial Biology of Cancer Evolution. Nat Rev Genet. 2023;24(5):295-313.
23. Riegel K, Yurugi H, Schlöder J, Jonuleit H, Kaulich M, Kirschner F, Arnold-Schild D, Tenzer S, Schild H, Rajalingam K. ERK5 modulates IL-6 secretion and contributes to tumor-induced immune suppression. Cell Death Dis. 2021 Oct 20;12(11):969.
24. Du T, Jia X, Dong X, Ru X, Li L, Wang Y, et al. Cosmc Disruption-Mediated Aberrant O-glycosylation Suppresses Breast Cancer Cell Growth via Impairment of CD44. Cancer Manag Res. 2020 Jan 22;12:511-22.
25. Shimizu K, Iyoda T, Okada M, Yamasaki S, Fujii SI. Immune suppression and reversal of the suppressive tumor microenvironment. Int Immunol. 2018 Sep 25;30(10):445-54.
26. Rogovskii V. Tumor-produced immune regulatory factors as a therapeutic target in cancer treatment. Front Immunol. 2024;15:1416458.
27. Gurusamy D, Clever D, Eil R, Restifo NP. Novel "elements" of immune suppression within the tumor microenvironment. Cancer Immunol Res. 2017;5(6):426-33.
28. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. Nat Immunol. 2002 Nov;3(11):991-8.
29. Valencia JC, Erwin-Cohen RA, Clavijo PE, Allen C, Sanford ME, Day CP, et al. Myeloid-Derived Suppressive Cell Expansion Promotes Melanoma Growth and Autoimmunity by Inhibiting CD40/IL27 Regulation in Macrophages. Cancer Res. 2021 Dec 1;81(23):5977-90.
30. Li S, Liu M, Do MH, Chou C, Stamatiades EG, Nixon BG, Shi W, Zhang X, Li P, Gao S, Capistrano KJ, Xu H, Cheung NV, Li MO. Cancer immunotherapy via targeted TGF-β signalling blockade in TH cells. Nature. 2020 Nov;587(7832):121-5.

31. Aguilera KY, Rivera LB, Hur H, Carbon JG, Toombs JE, Goldstein CD, Dellinger MT, Castrillon DH, Brekken RA. Collagen signaling enhances tumor progression after anti-VEGF therapy in a murine model of pancreatic ductal adenocarcinoma. Cancer Res. 2014 Feb 15;74(4):1032-44.
32. Ouyang W, O'Garra A. IL-10 family cytokines IL-10 and IL-22: from basic science to clinical translation. Immunity. 2019;50(4):871-91.
33. Youn JI, Collazo M, Shalova IN, Biswas SK, Gabrilovich DI. Characterization of the nature of granulocytic myeloid-derived suppressor cells in tumor-bearing mice. J Leukoc Biol. 2012 Jan;91(1):167-81.
34. Tie Y, Tang F, Wei Y, Wei X. Immunosuppressive cells in cancer: mechanisms and potential therapeutic targets. J Hematol Oncol. 2022;15(1):61.
35. Hinshaw DC, Shevde LA. The tumor microenvironment innately modulates cancer progression. Cancer Res. 2019;79(18):4557-66.
36. Taki M, Abiko K, Ukita M, Murakami R, Yamanoi K, Yamaguchi K, et al. Tumor Immune Microenvironment during Epithelial-Mesenchymal Transition. Clin Cancer Res. 2021 Sep 1;27(17):4669-79.
37. Batlle E, Massagué J. Transforming growth factor-β signaling in immunity and cancer. Immunity. 2019;50(4):924-40.
38. Briukhovetska D, Dörr J, Endres S, Libby P, Dinarello CA, Kobold S. Interleukins in cancer: from biology to therapy. Nat Rev Cancer. 2021 Aug;21(8):481-99.
39. Goel HL, Mercurio AM. VEGF targets the tumour cell. Nat Rev Cancer. 2013;13(12):871-82.
40. Barbera-Guillem E, Nyhus JK, Wolford CC, Friece CR, Sampsel JW. Vascular endothelial growth factor secretion by tumor-infiltrating macrophages essentially supports tumor angiogenesis, and IgG immune complexes potentiate the process. Cancer Res. 2002 Dec 1;62(23):7042-9.
41. Ma R, Sun JH, Wang YY. The role of transforming growth factor-β (TGF-β) in the formation of exhausted CD8+ T cells. Clin Exp Med. 2024 Jun 17;24(1):128.
42. Thomas DA, Massagué J. TGF-beta directly targets cytotoxic T cell functions during tumor evasion of immune surveillance. Cancer Cell. 2005;8(5):369-80.
43. Viel S, Marçais A, Guimaraes FS, Loftus R, Rabilloud J, Grau M, et al. TGF-β inhibits the activation and functions of NK cells by repressing the mTOR pathway. Sci Signal. 2016 Feb 16;9(415):ra19.
44. Choi SH, Cho HB, Choi JH, Kim HJ, Jang HJ, Cho S, et al. Nano-chemical priming strategy to enhance TGF-β resistance and anti-tumor activity of natural killer cells. J Control Release. 2024 Mar;367:768-78.
45. Caner A. Immune Escape Mechanism of Cancer. Curr Mol Biol Rep. 2023;10(1):1-11.
46. de Charette M, Marabelle A, Houot R. Turning tumour cells into antigen presenting cells: the next step to improve cancer immunotherapy? Eur J Cancer. 2016;68:134-47.
47. Garrido F, Algarra I. MHC antigens and tumor escape from immune surveillance. Adv Cancer Res. 2001;83:117-58.
48. Garrido F, Aptsiauri N, Doorduijn EM, Garcia Lora AM, van Hall T. The urgent need to recover MHC class I in cancers for effective immunotherapy. Curr Opin Immunol. 2016;39:44-51.
49. Bernd HW, Ziepert M, Thorns C, Klapper W, Wacker HH, Hummel M, et al. Loss of HLA-DR expression and immunoblastic morphology predict adverse outcome in diffuse large B-cell lymphoma—analyses of cases from two prospective randomized clinical trials. Haematologica. 2009;94(11):1569-80.
50. Roberts RA, Wright G, Rosenwald AR, Jaramillo MA, Grogan TM, Miller TP, et al. Loss of major histocompatibility class II gene and protein expression in primary mediastinal large B-cell lymphoma is highly coordinated and related to poor patient survival. Blood. 2006;108(1):311-8.
51. Leone P, Shin EC, Perosa F, Vacca A, Dammacco F, Racanelli V. MHC class I antigen processing and presenting machinery: organization, function, and defects in tumor cells. J Natl Cancer Inst. 2013;105(16):1172-87.
52. Yang K, Halima A, Chan TA. Antigen presentation in cancer- mechanisms and clinical implications for immunotherapy. Nat Rev Clin Oncol. 2023;20(9):604-23.
53. Stern LJ, Clement C, Galluzzi L, Santambrogio L. Non-mutational neoantigens in disease. Nat Immunol. 2024;25(1):29-40.
54. Rooney MS, Shukla SA, Wu CJ, Getz G, Hacohen N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. Cell. 2015;160(1-2):48-61.
55. Rosenthal R, Cadieux EL, Salgado R, Bakir MA, Moore DA, Hiley CT, et al. Neoantigen-directed immune escape in lung cancer evolution. Nature. 2019;567(7749):479-85.
56. McGranahan N, Rosenthal R, Hiley CT, Rowan AJ, Watkins TBK, Wilson GA, et al. Allele-Specific HLA Loss and Immune Escape in Lung Cancer Evolution. Cell. 2017;171(6):1259-71.e11.
57. Vázquez-García I, Uhlitz F, Ceglia N, Lim JLP, Wu M, Mohibullah N, et al. Ovarian cancer mutational processes drive site-specific immune evasion. Nature. 2022;612(7941):778-86.
58. Lin W, Chen L, Zhang H, Qiu X, Huang Q, Wan F, et al. Tumor-intrinsic YTHDF1 drives immune evasion and resistance to immune checkpoint inhibitors via promoting MHC-I degradation. Nat Commun. 2023 Jan 17;14(1):265.
59. Wu X, Li T, Jiang R, Yang X, Guo H, Yang R. Targeting MHC-I molecules for cancer: function, mechanism, and therapeutic prospects. Mol Cancer. 2023 Dec 2;22(1):194.

60. Kawase K, Kawashima S, Nagasaki J, Inozume T, Tanji E, Kawazu M, et al. High Expression of MHC Class I Overcomes Cancer Immunotherapy Resistance Due to IFNγ Signaling Pathway Defects. Cancer Immunol Res. 2023 Jul 5;11(7):895-908.
61. Knaus HA, Berglund S, Hackl H, Blackford AL, Zeidner JF, Montiel-Esparza R, et al. Signatures of CD8+ T cell dysfunction in AML patients and their reversibility with response to chemotherapy. JCI Insight. 2018;3(21):e120974.
62. Tettamanti S, Pievani A, Biondi A, Dotti G, Serafini M. Catch me if you can: how AML and its niche escape immunotherapy. Leukemia. 2022 Jan;36(1):13-22.
63. Toffalori C, Zito L, Gambacorta V, Riba M, Oliveira G, Bucci G, et al. Immune signature drives leukemia escape and relapse after hematopoietic cell transplantation. Nat Med. 2019;25(4):603-11.
64. Christopher MJ, Petti AA, Rettig MP, Miller CA, Chendamarai E, Duncavage EJ, et al. Immune escape of relapsed AML cells after allogeneic transplantation. N Engl J Med. 2018;379(24):2330-41.
65. Kline DE, MacNabb BW, Chen X, Chan WC, Fosco D, Kline J. CD8α+ dendritic cells dictate leukemia-specific CD8+ T cell fates. J Immunol. 2018;201(12):3759-69.
66. Baghban R, Roshangar L, Jahanban-Esfahlan R, Seidi K, Ebrahimi-Kalan A, Jaymand M, et al. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Commun Signal. 2020 Apr 7;18(1):59.
67. Cheng B, Yu Q, Wang W. Intimate communications within the tumor microenvironment: stromal factors function as an orchestra. J Biomed Sci. 2023;30(1):1.
68. Di Tacchio M, Macas J, Weissenberger J, Sommer K, Bähr O, Steinbach JP, et al. Tumor Vessel Normalization, Immunostimulatory Reprogramming, and Improved Survival in Glioblastoma with Combined Inhibition of PD-1, Angiopoietin-2, and VEGF. Cancer Immunol Res. 2019;7(12):1910-27.
69. Choueiri TK, Eto M, Motzer R, De Giorgi U, Buchler T, Basappa NS, et al. Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the phase 3, randomised, open-label study. Lancet Oncol. 2023;24(3):228-38.
70. Zehravi M, Maqbool M, Ara I. Curcumin – A promising phytocompound of immense potential. Adv J Chem B. 2021;3(4):271-82.
71. Abd Al-ameer AM, Abdulazeem L, Kzar MH, Khattab ES, Naje AS. Mechanism of Immune System for Evading and Escaping Cancer Cells: A Brief Review. J Med Chem Sci. 2023;6(8):1843-50.
72. Mansuri N, Hashimi H, Matilainen M, Alzgheid A, Alsagher M, Jbireal JM, et al. Breast Cancer Molecular Subtypes in Libyan Women: Incidence and Prognostic Value of Securin and Separase. Alq J Med App Sci. 2025;8(3):2132-43.
73. Gonzalez H, Hagerling C, Werb Z. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes Dev. 2018;32(19-20):1267-84.
74. Sadeghalvad M, Mohammadi-Motlagh H-R, Rezaei N. Immune microenvironment in different molecular subtypes of ductal breast carcinoma. Breast Cancer Res Treat. 2021;185(2):261-79.
75. Del Gil CR, Huh SJ, Ekram MB, Trinh A, Liu LL, Beca F, et al. Immune escape in breast Cancer during in situ to Invasive Carcinoma Transition. Cancer Discov. 2017;7(10):1098-115.
76. Salemme V, Centonze G, Cavallo F, Defilippi P, Conti L. The Crosstalk between Tumor Cells and the Immune Microenvironment in breast Cancer: implications for Immunotherapy. Front Oncol. 2021;11:610303.
77. Arner EN, Rathmell JC. Metabolic programming and immune suppression in the tumor microenvironment. Cancer Cell. 2023;41(3):421-33.
78. Nicolini A, Ferrari P. Involvement of tumor immune microenvironment metabolic reprogramming in colorectal cancer progression, immune escape, and response to immunotherapy. Front Immunol. 2024;15:1353787.
79. Li AM, Ye J. Deciphering the Warburg effect: metabolic reprogramming, epigenetic remodeling, and cell dedifferentiation. Annu Rev Cancer Biol. 2024;8:1-24.
80. Enríquez JA, Mittelbrunn M. Warburg effect reshapes tumor immunogenicity. Cancer Res. 2024;84(12):2043-5.
81. Kareva I, Hahnfeldt P. The emerging "hallmarks" of metabolic reprogramming and immune evasion: distinct or linked? Cancer Res. 2013;73(9):2737-42.
82. Zhang X, Song W, Gao Y, Zhang Y, Zhao Y, Hao S, Ni T. The Role of Tumor Metabolic Reprogramming in Tumor Immunity. Int J Mol Sci. 2023 Dec 13;24(24):17422.
83. Xia L, Oyang L, Lin J, Tan S, Han Y, Wu N, et al. The cancer metabolic reprogramming and immune response. Mol Cancer. 2021 Feb 5;20(1):28.
84. Herbel C, Patsoukis N, Bardhan K, Seth P, Weaver JD, Boussiotis VA. Clinical significance of T cell metabolic reprogramming in cancer. Clin Transl Med. 2016 Dec;5(1):29.
85. Drake CG, Jaffee E, Pardoll DM. Mechanisms of Immune Evasion by Tumors. Adv Immunol. 2006;90:51-81.
86. Stark MC, Joubert AM, Visagie MH. Molecular Farming of Pembrolizumab and Nivolumab. Int J Mol Sci. 2023;24(12):10045.
87. Krasniqi E, Barchiesi G, Pizzuti L, Mazzotta M, Venuti A, Maugeri-Saccà M, et al. Immunotherapy in HER2-positive breast cancer: state of the art and future perspectives. J Hematol Oncol. 2019;12(1):111.
88. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for early triple-negative breast Cancer. N Engl J Med. 2020;382(9):810-21.

89. Kalia M, Bhavya K, Pal D. Tumor Microenvironment Regulates Immune Checkpoints: Emerging Need of Combinatorial Therapies. Curr Tissue Microenviron Rep. 2024;5(1):1-11.
90. Nuccio A, Viscardi G, Cameron R, Salomone F, Servetto A, Venanzi FM, et al. 118P Role of PD-L1 and pathological complete response (pCR) with neoadjuvant (NEO) or perioperative (PERIOP) immune-checkpoint inhibitors (ICI) and platinum-based chemotherapy (PCT) in resectable non-small cell lung cancer (NSCLC): a systematic review and metanalysis. ESMO Open. 2024;9:102697.
91. Krishnamurthy N, Nishizaki D, Lippman SM, Miyashita H, Nesline MK, Pabla S, et al. High CTLA-4 transcriptomic expression correlates with high expression of other checkpoints and with immunotherapy outcome. Ther Adv Med Oncol. 2024;16:17588359241236287.
92. Cheng W, Kang K, Zhao A, Wu Y. Dual blockade immunotherapy targeting PD-1/ PD-L1 and CTLA-4 in lung cancer. J Hematol Oncol. 2024;17(1):54.
93. Daei Sorkhabi A, Mohamed Khosroshahi L, Sarkesh A, Mardi A, Aghebati-Maleki A, Aghebati-Maleki L, et al. The current landscape of CAR T-cell therapy for solid tumors: mechanisms, research progress, challenges, and counterstrategies. Front Immunol. 2023;14:1113882.
94. Manieri NA, Chiang EY, Grogan JL. TIGIT: a key inhibitor of the cancer immunity cycle. Trends Immunol. 2017;38(1):20-8.
95. Yu X, Harden K, Gonzalez LC, Francesco M, Chiang E, Irving B, et al. The surface protein TIGIT suppresses T cell activation by promoting the generation of mature immunoregulatory dendritic cells. Nat Immunol. 2009 Jan;10(1):48-57.
96. Liu S, Sun Q, Ren X. Novel strategies for cancer immunotherapy: counter-immunoediting therapy. J Hematol Oncol. 2023;16(1):38.
97. Strebhardt K, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. Nat Rev Cancer. 2008;8(6):473-80.
98. Karlitepe A, Ozalp O, Avci CB. New approaches for cancer immunotherapy. Tumour Biol. 2015;36(6):4075-8.
99. Liu J, Fu M, Wang M, Wan D, Wei Y, Wei X. Cancer vaccines as promising immuno-therapeutics: platforms and current progress. J Hematol Oncol. 2022 Mar 18;15(1):28.
100. Lin MJ, Svensson-Arvelund J, Lubitz GS, Marabelle A, Melero I, Brown BD, Brody JD. Cancer vaccines: the next immunotherapy frontier. Nat Cancer. 2022 Aug;3(8):911-26.
101. Çağrı Ş, Halit C, Kenan İ. Kanser İmmün Terapi ve Monoklonal Antikorlar. Fırat Üniv Sağlık Bilimleri Tıp Derg. 2013;27(2):105-10.
102. Chen Y, Xin Q, Zhu M, Qiu J, Li R, Tu J. Trogocytosis in CAR immune cell therapy: a key mechanism of tumor immune escape. Cell Commun Signal. 2024;22(1):521.