IBN SINA

Ibn Sina Journal of Medical Science, Health & Pharmacy
Vol. 4, No. 3, 2026, pp. 1-27
ISSN 3104-6428
https://ibn-sina-journal-of-medical-sciences.jo

# Immune escape mechanisms and new strategies for treatment in immune cell behavior in the tumor setting

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DOI: https://doi.org/10.64440/IBNSINA/SINA0017

**ARTICLE INFO**

**Article history**
Received Feb 08, 2026
Revised Feb 10, 2026
Accepted Mar 11, 2026

**Keywords**
Immune Escape;
Immunotherapy;
Tumor Microenvironment;
Immune Cells.

**ABSTRACT**

Background: Tumor microenvironment (TME) is an essential factor in tumor growth, immune system evasion, as well as the failure of immunotherapy. Mutual influence of cancer and immune cells is responsible for the formation of a complex immunosuppressive milieu that, in turn, seriously hampers the impact of the current anti, cancer treatments. To figure out how immune escape is at work in the TME is a prerequisite for the designing of the more powerful immunotherapy drugs/fragments.

Methods: For this work, we integrated a number of methods both in silicon and in the lab for the identification of tumor microenvironment mechanisms of immune escape using a corpus of recently conducted experimental and clinical studies obtained from PubMed and Scopus databases. We initially identified 150 research articles, then based on our inclusion criteria we proceeded with 45 of them and those formed the basis of our final comparative mechanistic analysis.

Results: Our investigation reveals tumor cells not only shifting the microenvironment but also luring immunosuppressive cells like tumor, associated macrophages (TAMs) and regulatory T cells (Tregs). They are at the same time causing metabolic stresses like hypoxia, acidosis, and lack of nutrients. All these impair the functioning of the cytotoxic CD8 T cells and natural killer (NK) cells, and at the same time, activate immune checkpoints. Novel therapies aimed at immune checkpoints, macrophage polarization, immunometabolic pathways, and cellular therapies such as CAR, T cells are quite promising in challenging tumor, induced immune suppression.

Conclusion: Cancer immune evasion is a result of a complex network of cellular, molecular, and metabolic interactions within the tumor microenvironment and not just a single pathway. Therapies that hit several parts of this ecosystem at once might be a better strategy to improve the clinical results of cancer immunotherapy.

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## 1. Introduction

The immune system is essentially a very well organized network of cells and molecules that work together to recognize and get rid of unhealthy or cancerous cells. The idea of immunosurveillance in tumor immunology is one of the key principles that refers to immune cells' capacity to find and kill the transformed cells before they become tumors visible to the naked eye. However, more and more data points out that a large number of tumors come up with very tricky ways that allow them not to be recognized by the immune system. The tumor microenvironment (TME) has become known as a major factor in tumor growth and how well the therapy works. Instead of being just an inactive arrangement https://pravasijuana.com/ that supports the structure of the tumor, the TME is a living community of tumor cells, immune cells, support cells, parts of extracellular matrix, and signaling molecules in solution. These factors are in ongoing interaction and together they determine tumor https://marijuanabudget.com/ growth, immune suppression, and therapy resistance [1]. The idea of tumor immunosurveillance was first put forward by Burnet and Thomas in the mid, 1900s. According to this hypothesis, the immune system, especially lymphocytes, is constantly checking the tissues to find and get rid of cells that have become cancerous [2]. That hypothesis was later supported by the model of immunoediting which Rob Schreiber and his team put forth which details a dynamic 3 stage process of Elimination, Equilibrium, and Escape [3]. In the last stage cancer cells develop ways to either avoid the immune systems notice all together or to resist the immune attack which is what allows them to grow out of control and form a clinical tumor [4].

Tumor development occurs within a complex biological context known as the tumor microenvironment, which consists of interacting cellular, molecular, and structural components that influence tumor behavior (TME). The tumor microenvironment is now recognized as a dynamic and functionally active ecosystem that critically regulates tumor progression, immune evasion, and therapeutic response [5]. The tumor microenvironment is a very dynamic system which is made up of a complex web of cellular and non-cellular elements; To the list of cancer cells, we add a variety of immune cells (like macrophages, neutrophils, lymphocytes) and stromal cells “cancer associated fibroblasts – CAFs”, components of the cell's external matrix, and a large array of signaling agents (cytokines, growth factors), and also, we see in its unique physiochemical features like hypoxia and acidosis. It is in the back and forth between the tumor and these players that we see the determination of the immune response’s fate. As the tumor does attract some of these elements to fuel its growth and spread, also in that same interaction some of them are used to bring about the tumors defeat [6].

Immunotherapies which include antibodies to the receptor programmed death protein 1 (PD-1) and its ligand (PD-L1), and also, to cytotoxic T cell associated protein 4 (CTLA-4) have seen a paradigm, shift in cancer treatment we see play out. This, in 2018 saw James Allison and Tasuku Honjo, awarded the Nobel Prize in Medicine. What we’ve got is a transformation in how we think of cancer treatment – we are seeing amazing clinical responses in some tumor types like melanoma and non-small cell lung cancer, that are very durable [7].

Despite these remarkable clinical advances, significant limitations remain, including primary resistance to immunotherapy and the development of acquired resistance during treatment. To start with we see large scale primary resistance in which up to 80% of patients do not respond at all to

immune checkpoint inhibitor treatment. Also, we have acquired resistance in some patients which see an initial response but then the tumor comes back. At root of these issues is the tumor microenvironment which we see to play a key role [8]. This is a challenge to present day science which assumes that successful therapy is a result of just T cell activation – in fact we also must pay attention to the tumor's environment which we must make more permeable for the T cells and which must support their function. The tumor microenvironment with its very complex and sometimes overlapping mechanisms puts up an immune barrier to attack. It does this by attracting in suppressor immune cells like regulatory T cells and M2 type TAMs, by putting up a physical barrier via fibroblasts and extracellular matrix, and by creating a very tough metabolic environment which in turn weakens killer cell [9].

The tumor microenvironment has emerged as a central determinant of immune escape and therapeutic resistance in cancer. Consequently, understanding the complex interactions between tumor cells and immune components within this ecosystem is essential for the development of next-generation immunotherapies. This research we are presenting here does an important theoretical job in that we are bringing together and looking at present day scientific data to put forth a whole picture of how we may turn the tumor microenvironment from a tumor's ally into a target for therapy which in turn will lead to more intelligent and personalized treatment options.

Despite extensive research on tumor immunology, a comprehensive analytical framework integrating immune suppression mechanisms within the tumor microenvironment with emerging therapeutic strategies remains necessary, which also reviews the latest in therapy in an integrated way and which also ties in to the features of the tumor microenvironment itself. Many reviews at present either focus in on the detail of the mechanism or of the therapy separate from each other, or they may look at one cell type or one path way. What is missing is a theoretical study which puts forth a big picture which goes from breaking down the tumor microenvironment, to looking at the interplay with immune cells, to what that means for which elements to target therapeutically and also what the relationships between them are.

This study investigates the interactions between immune cells and tumor microenvironment components to better understand the mechanisms underlying tumor-mediated immune escape. Also, we are trying to determine how these relationships produce an immunosuppressive environment which in turn makes the tumor resistant to attacks from the body. And we will also look at new and developing therapeutic approaches – especially of the combination therapy variety at which we aim to give reason and a foundation for them; and the goal is what is the primary question, how to change the tumor microenvironment so as to better the effects of immunotherapy and to also get over resistance issues.

## 2. Method

### 2.1. Study Design

Study Design

This research employed an integrative analytical research framework to investigate immune escape mechanisms within the tumor microenvironment and their implications for cancer immunotherapy. The study combines mechanistic interpretation, comparative pathway analysis, and cross-study synthesis of experimental and clinical evidence to identify key biological drivers of tumor-mediated immune suppression.

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**Dataset Construction**

A structured dataset was constructed from the 45 eligible studies to facilitate comparative mechanistic analysis. Extracted variables included cancer type, immune escape mechanism, involved immune cell populations, metabolic factors, and proposed therapeutic targets. This dataset enabled systematic comparison of biological mechanisms contributing to tumor immune evasion.

**Data Analysis**

Selected studies were analyzed to identify recurring mechanistic pathways involved in immune escape. These pathways were categorized into four major groups:

Cellular immunosuppressive mechanisms

Metabolic and physicochemical alterations in the tumor microenvironment

Immune checkpoint signaling pathways

Emerging therapeutic strategies targeting TME components

Comparative analysis was performed to identify common mechanisms and potential therapeutic vulnerabilities within the tumor microenvironment.

Which target the interaction between immune cells and TME elements. A structured evidence screening workflow was implemented to ensure transparent identification, evaluation, and synthesis of relevant studies. The workflow included database search, duplicate removal, eligibility screening, and final study inclusion to support reproducibility of the analytical process [10].

## Mechanistic Comparative Analysis

To strengthen the analytical framework of the study, the selected literature was further examined using a comparative pathway analysis. Mechanisms identified in the included studies were categorized into four principal biological domains: cellular immunosuppressive networks, metabolic alterations within the tumor microenvironment, immune checkpoint signaling pathways, and emerging therapeutic intervention strategies. This analytical categorization enabled identification of recurrent mechanistic patterns across multiple cancer types and allowed the mapping of potential therapeutic targets within the tumor microenvironment.

### 2.2. Analytical Framework

To identify key drivers of tumor immune escape, the selected studies were further analyzed using a comparative pathway framework. Mechanisms described in the literature were grouped into four major biological domains:

1. Cellular immunosuppressive networks
2. Metabolic constraints within the tumor microenvironment
3. Immune checkpoint signaling pathways
4. Emerging therapeutic intervention strategies

This framework allowed identification of recurring mechanistic patterns and potential therapeutic vulnerabilities across different cancer types.

### 2.3. Information Sources and Search Strategy

In December 2025 to March 2026, we did a through electronic search in the two main databases, PubMed and Scopus. We chose these databases for their in-depth coverage of published research in life sciences, medicine, and clinical sciences [11]. Our search strategy was to identify studies published in English between January 2024 and March 2026 which we did in order to present an analysis of the latest scientific data in a very dynamic field.

We developed a wide-ranging search approach that included a set of terms which we identified as relevant to our research question – we also used Medical Subject Heading terms from the field. We put together a very detailed search which included the use of AND, and OR Boolean operators in order to increase our sensitivity and accuracy [12]. We looked at key terms like “tumor microenvironment”, “immune escape”, “immunotherapy”, “TAMs”, “Tregs”, “checkpoint inhibitors” as well as related terms which included “hypoxia”, “metabolism” and “resistance mechanisms”.

### 2.4. Inclusion and Exclusion Criteria

In the present study we pre-determined the inclusion and exclusion criteria which in turn helped us to focus on the most relevant and reliable studies as recommended by the PICOS framework for analytical research studies [13], which includes Population, Intervention, Comparison, Outcome, and Study Design.

In our study we have included:

– Field of study: Research which looks at the interactions between the immune system and tumor microenvironment, and which present therapeutic approaches that target this interaction.

– Type of study: We included original peer reviewed research which is preclinical in nature, results from clinical trials (phases I to III), analytical research studies, and meta-analyses.

– Time frame: We looked at studies which were between January 2024 and March 2026.

Exclusion of the following:

– Topic: which look at pharmacological therapeutic effects but do not address the base mechanisms of TME.

– Also, we excluded Study Type: opinion pieces, editorials, case reports, conference abstracts and the studies published before January 2024

### 2.5. Study Selection Mechanism

Between January 2024 and March 2026, we identified 150 initial studies via a search of the PubMed and Scopus databases. Out of which we removed 25 duplicates to be left with 125 unique studies. We went through the studies’ titles and abstracts which had our pre-determined selection and exclusion criteria and we ended up excluding 50 of them. Of the 25 we excluded, 13 didn’t look at the interaction between immune cells and tumor microenvironment. Also, we excluded 15 that looked at general immune mechanisms but didn’t in depth look at the TME. We also had to put out of the running 10 which were outside our specified time frame (before 2024).

After the first round of screening, we conducted the in-depth Full Text Eligibility which took in 75 studies for a final go / no go. In the end 30 were out – 12 of which were what we determined to be opinion pieces or editorials rather than primary reports. Also 10 did not have enough data put

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forth on the issue of immune escape at a molecular level. Also, we saw 8 that looked at very specific cancer types and failed to present the broad scope we required.

A total of 45 studies met the predefined analytical inclusion criteria and were incorporated into the final dataset used for mechanistic and comparative analysis. These studies provided experimental, translational, and clinical insights into immune escape pathways and therapeutic targeting strategies within the tumor microenvironment. The study identification and eligibility workflow is summarized in Figure 1, illustrating the analytical screening process used to construct the final dataset, which in turn also provides full transparency of the study numbers at each stage.

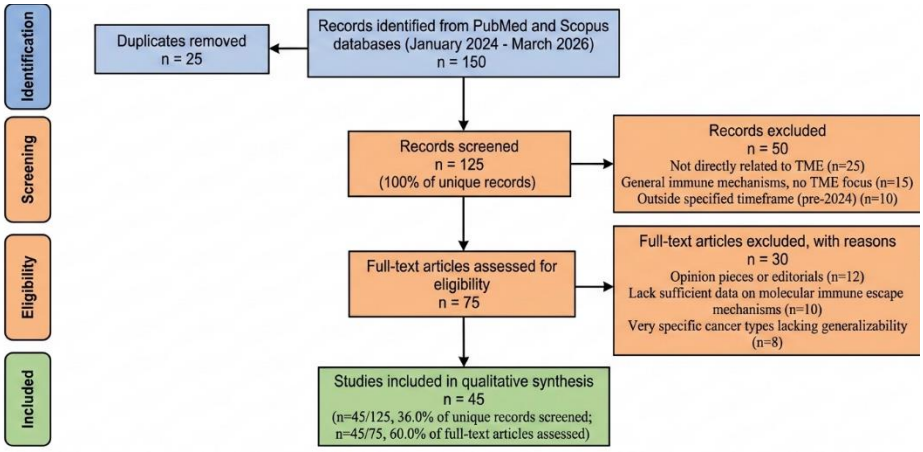


**Fig. 1.** In the PRISMA 2020 flow chart which we present Studies included in our analysis of the tumor microenvironment and immune escape from it - Representative studies included in the analysis are summarized in Table 1.

**Table 1.** Summary of representative studies investigating immune escape mechanisms within the tumor microenvironment.

| Author | Year | Cancer Type | Immune Escape Mechanism | Key Findings |
|---|---|---|---|---|
| **Sharma et al.** | 2024 | Multiple cancers | Chemotherapy-induced immune modulation | Chemotherapy can both suppress and stimulate immune responses depending on treatment context. |
| **Bell & Zou** | 2024 | Solid tumors | Resistance to PD-1/CTLA-4 blockade | Identified multiple resistance pathways including metabolic suppression and immune exhaustion. |
| **Huang et al.** | 2025 | Solid tumors | Tumor microenvironment remodeling | Tumor-associated macrophages promote immune suppression and tumor progression. |
| **Dakal et al.** | 2024 | Various cancers | Tumor infiltrating immune cells | Immune cell composition strongly predicts treatment response. |
| **Wang et al.** | 2025 | Lung cancer | PD-1 resistance pathways | Combination therapy targeting multiple checkpoints improves response rates. |
| **Huang** | 2025 | Multiple | Immune evasion | Multi-omics approaches reveal |

| | | | | |
|---|---|---|---|---|
| **et al.** | | cancers | pathways | mechanisms of immune escape in cold tumors. |
| **Zhu et al.** | 2026 | Leukemia | Immune evasion signaling | Tumor microenvironment signaling pathways influence therapy resistance. |
| **Wen et al.** | 2026 | Solid tumors | CAR-T engineering strategies | Programmable CAR-T cells improve tumor targeting and survival in hostile microenvironments. |
| **Gong et al.** | 2026 | Leukemia | CRISPR-engineered CAR-T cells | Gene editing improves CAR-T persistence and resistance to inhibitory signals. |

## 3. Tumor Microenvironment – TME

Tumors today are seen past their simple masses of cancer cells. We have a shift in what we think of as the tumor microenvironment TME [14], which in turn is a game changer in tumor biology [15]. This concept of TME is that of a dynamic and complex ecosystem which is the home to the tumor – made up of a very intricate network of cellular and non-cellular elements which are in constant interaction with cancer cells and each other [16]. This environment is not a static background; it is a dynamic player in the tumor's fate [17]. It may put up a natural barrier to tumor growth or it may become a support structure for tumor survival, growth and spread [17]. To really understand this environment in total is the first and most important step in to figuring out immune escape mechanisms and in turn in to developing successful therapies [18].

### 3.1. Cellular Components

In the tumor microenvironment we see a great deal of cell diversity which includes cancer cells as well as many different types and origins of normal cells [19]. What we have is a complex balance of interactions between them which in turn gives the microenvironment a pro or anti-tumor role [20]

#### 3.1.1. The Cancer Cells Themselves

Cancer cells make up the core of what we see in this ecosystem and they are the primary drivers [21]. Cancer cells are not merely abnormal proliferating cells; rather, they actively remodel their surrounding microenvironment to promote tumor survival, immune evasion, and metastatic progression [22]. Cancer cells put out a wide range of signals (for instance cytokines and growth factors) which they use to:

- Recruit immune cells: Draw in a variety of immune cells to the tumor site, instead of killing them we coopt them into our side [23].

- In some cases, normal cells are coaxed into becoming cancer associated fibroblasts which we term CAFs, we also observe the suppression of immunity by innate and adaptive immune cells that are reprogrammed more effectively [24].

- Alteration of the extracellular matrix: we see that enzymes are put out which in turn supports cancer cell invasion and spread through modification of the extracellular matrix [25].

Also, cancer cells present high genomic instability which in turn gives rise to various subtypes that have different functions – for instance the ability to adapt to environmental stress like hypoxia or to become resistant to treatments [26].

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ISSN 3104-6428
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Ibn Sina journal Of Medical Science, Health & Pharmacy

### 3.1.2. Innate immune cells

Innate immune cells, which are the first to respond and which make up the first line of defense do in the tumor microenvironment what is almost a180 degree turn from what is their normal function – they take on roles which are at odds with what they are supposed to do [27].

- In the tumor microenvironment macrophages, are the most abundant of immune cells [28]. These macrophages are drawn to the tumor by chemokines like CCL2 and CSF-1 [29]. Instead of turning into the pro-tumor M1 type which causes inflammation and death of cancer cells, in the tumor microenvironment macrophages, for the most part turn into the alternative M2 type which is influenced by cytokines like IL-4, IL-13, and TGF – beta [30]. M2 macrophages play a number of roles in supporting tumors; they produce growth factors (like EGF) that promote cancer cell division, secrete angiogenic factors (as VEGF), In addition, they release inhibitory cytokines "IL-10, TGF-beta" [24], in order to inhibit cytotoxic T cells and the expression of the PD-L1 immune checkpoint [25].

- Tumor associated neutrophils (TANs) like macrophages present in two forms – the anti-tumor N1 which is a good guy and the pro-tumor N2 which is a bad guy [31]. In the tumor microenvironment, TGF-β is a key player that pushes neutrophils into the N2 phenotype which in turn causes immunosuppression, promotes growth of new blood vessels and also helps cancer cells to break away and spread [32].

- Mast cells which tend to congregate at the tumor periphery also secrete a wide variety of mediators that include histamine, proteases and cytokines such as TGF-β and VEGF [33]. These release products in turn play a role in breaking down the extracellular matrix, this includes suppressing the local immune response, along with stimulating the growth of new blood vessels [34].

- Natural killer cells; which are a special case of innate cells, usually don't require prior exposure to a pathogen to go into action; instead, they will directly attack cancer cells. But what the tumor does in its environment is try to shut down that natural killer action [35]. Through hypoxia, the release of substances like TGF beta and PGE2 and also the presentation of what we call inhibitory ligands to receptors on the NK cells – that's done out of the cancer cells' interest but also some other suppressor cells' interest as well – what we see is a shutting down, a paralysis if you will, of the natural killer function and a reduction in their numbers at the tumor site [36].

### 3.1.3. Tissue responsive immune cells

Adaptive immune cells, which make up the specialized branch of "the immune system" that has the ability to produce specific responses, and also forms the immune memory – in the tumor microenvironment we see a play out between pro-tumor and anti-tumor cells which include [37]:

- T Cells: we have the most info on these in terms of the tumor microenvironment which we also refer to as the tumor's local environment – also we see that T cells fall into a few main groups [38]:

A. Cytotoxic CD8+ T Cells are the primary players in the body's anti-tumor response, which identify cancer antigens and kill the tumor cells which present them [39]. But in the tumor microenvironment what we see is a different picture here these cells are put under great stress from constant stimulation and also from a suppressive environment. What results is T cell exhaustion which sees these cells lose their ability to divide and produce cytotoxic cytokines like IFN- gamma and TNF alpha – also we see expression of immune checkpoints like PD-1 at high levels on the surface of these exhausted cells [40].

B. Helper T cells (CD4+ T cells) play many roles in immune response. For example, Th1 type cells which are involved in anti-tumor cellular response, also other types of these cells like Th2 and Th17 in some settings support tumor growth [41].

C. In the T cell family Regulatory T cells (Tregs) are the primary tumor associated cells [42]. Tregs are drawn into the tumor microenvironment by chemicals like CCL22 or they develop there from local TGF-β [43]. Also, Tregs play a suppressive role in the "immune system" via many routes. They produce inhibitory cytokines (IL-10, TGF-beta), which in turn dampen the immune response also they use up IL-2 which is a requirement for the activity of cytotoxic T cells, and they present the expression of inhibitory receptors like CTLA-4 which in turn bind to and disable co-stimulatory molecules on antigen presenting cells [44].

- B cells: In the past years, the issue of what B cells do in the tumor microenvironment has been very much up for discussion [45]. We have seen that B cells, which produce antibodies play a role in enhancing the immune response, but recent research reports that certain B cell subsets which we term BREGs play a suppressive role by way of producing "IL-10 and TGF-β", and also in the promotion of regulatory T cell development [46].

### 3.1.4. Stromal Cells

In tumors stromal cells make up the support structure which in turn plays a key role in the creation of the tumor's physical, and chemical microenvironment [47]. They include:

- In many solid tumors, Cancer Associated Fibroblasts (CAFs) are the most prevalent stromal component [48]. From the activation of normal fibroblasts, or other sources like smooth muscle cells, they arise [49]. Cancer cells and inflammation play a role in the activation, which turns these fibroblasts into active CAFs that in turn produce great amounts of extracellular matrix components like collagen, growth factors such as HGF and EGF, and immunostimulating cytokines like TGF – beta and CXCL12 [50]. Also, CAFs play a role in the formation of a physical barrier, which in turn impairs immune cell access. They promote "cancer cell" survival and proliferation and also support angiogenesis [51].

Tumors use CAFs to put up a physical barrier which in turn causes immune cells' access to be an issue, also they promote cancer cell survival and growth and support angiogenesis [52]. In addition, it's the endothelial cells which line the tumor's blood vessels thus serving as the gateways for immune cells, nutrients and oxygen in and cancer cells out [53]. But within the tumor these blood vessels are usually abnormal in structure and function; they are convoluted and leaky and also express different adhesion molecules [54]. This abnormal vasculature causes ischemia (hypoxia and acidosis) which in turn impairs immune cells' movement into the tumor (infiltration) [55]. Also, the endothelial cells themselves put out immune checkpoint ligands which in turn cause immunosuppression [56].

## 3.2. Non-Cellular Components

Also, in addition to cellular diversity the tumor microenvironment has non-living elements which form the setting for chemical and physical interaction between cells, and in turn play a key role in determining cell behavior [57].

### 3.2.1. Extracellular Matrix

The extracellular matrix (ECM), which is a complex 3D network of macromolecules that fill in the spaces between cells [58]. It is mostly made up of structural proteins like collagen, and elastin adhesive proteins like fibronectin, and laminin and proteoglycans [15]. In the tumor microenvironment what we see is the ECM goes through radical changes thanks to cancer cells and cancer associated fibroblasts which in turn cause increased rigidity and thickness [25]. This "restructured ECM" plays many roles:

- Physical Barriers which we see as almost a perfect wall against the immune cells, especially the cytotoxic T cells – which are unable to get to the cancer cells or into the tumor [17].

- Physical barrier which is a dense wall that keeps out immune cells in particular cytotoxic T cells and from getting into the tumor [20]. Also, we see that the extracellular matrix is a stimulator of mechanical signals within cancer cells and also cancer associated fibroblasts which in turn promotes their survival and growth [24].

- Soluble factor reservoir: the extracellular matrix in which malleus is embedded serves as a storage and release site for growth factors and cytokines as needed and in doing so it regulates cell behavior [29].

### 3.2.2. Chemical Signals

In the tumor microenvironment, there is a complex network of soluble factors which serve as the "language of communication" between cells [32]. Which factors include:

- Cytokines are small protein molecules that act as messengers between immune cells [35]. In tumor environment what we see is a preponderance of the inhibitory kind of cytokine action which includes high levels of IL-10, and TGF-β that in turn suppress cytotoxic cell activity, and promote regulatory cell activity – at the same time we see a reduced action of stimulatory cytokines like IFN-gamma and IL-2 [38].

- Chemokines are a group of cytokines that have the specialization of directing cell movement [41]. In the case of chemokines like CCL2, CCL5, and CXCL12 we see that they attract what are called inhibitory immune cells into the tumor microenvironment (for example TAMs, Tregs, and MDSCs) which isn't good [43]. Also, we see that the attraction of what are for instance chemokines CXCL9 and CXCL10 which bring in the cytotoxic cells is in some cases lessened [45]. Chemokines plays a role in the regulation of cell movement [47].

- Growth factors play a key role in which cancer cells, and associated fibroblasts are very active in producing, for example VEGF which we know triggers angiogenesis, EGF which in turn stimulates cell division, and TGF-β which has many functions but mainly is in charge of immunosuppression and promoting what is known as the epithelial to mesenchymal transition or EMT [49].

### 3.2.3. Physicochemical Conditions

In the tumor microenvironment we see to have very different physical and chemical conditions as compared to healthy tissues which in turn produces selective stresses on all cells in that environment [51]. These include:

- Tumors grow fast and develop abnormal blood vessels which in turn cause serious oxygen depletion which we see in large hypoxic areas [53]. In response to hypoxia cells stabilize and activate HIF-1 alpha [54]. This factor in turn switches on genes which help cancer cells to adapt to low oxygen (for instance those which support anaerobic glycolysis) and which promote cell survival [55]. Also, HIF-1 alpha increases VEGF expression which in turn causes more abnormal angiogenesis, at the same time cytotoxic and natural killer T cell function and promoted M2 macrophage differentiation [56].

- In that which cancer cells shift to glucose metabolism through anaerobic glycolysis which in fact is seen when they are in the presence of oxygen (what Warburg put forth) they produce large amounts of lactic acid which in turn lowers the tumor microenvironment's pH (acidosis) [57]. This acidic setting is toxic to certain immune cells like cytotoxic T cells and natural killer cells, which in turn see a suppression of their growth, cytokine production, and ability to do their job. Also, this

environment of acid stimulates cancer associated fibroblasts to change the extracellular matrix and at the same time it also causes macrophages to take on a more inhibitory role [14].

- Nutrient depletion is a feature of many growing tumors, what we see is a speed up of cancer cell growth along with a reduction in blood supply to the tumor microenvironment [15]. In that setting, key nutrients like glucose, glutamine, and also essential amino acids, we see a large-scale depletion of these, which in turn creates a very competitive environment in which the adaptable cancer cells out do everything else, at the same time we see our immune cells which require great amounts of energy to do their job are left without the fuel they need, which in turn causes them to either slow down or die [16]. Fig. 2 shows a comprehensive diagram showing the tumor environment (which is also known as TME), as a complex ecosystem.

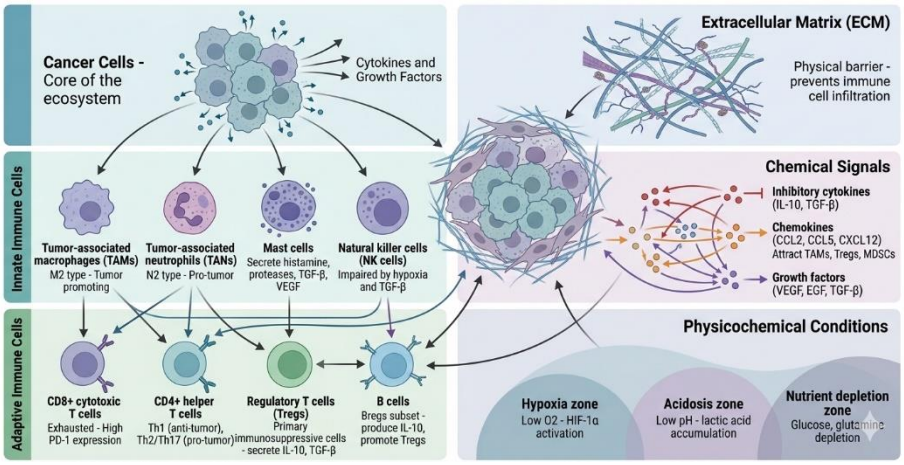


**Fig. 2.** Tissue and non-tissue elements of the tumor microenvironment which includes

### 3.3. Tumor Microenvironment as a Tumor Incubator: from surveillance to support

Upon review of the various cellular and noncellular components that which the tumor microenvironment is made up of it is clear that the issue at hand is far greater than simply a location for tumor development [17]. In fact, this environment has transformed into a very active and key player in tumor progressions [18]. The tumor microenvironment is no longer viewed solely as a site where immune cells eliminate malignant cells; rather, it is increasingly recognized as a complex ecosystem that can be reprogrammed to support tumor growth and immune evasion [19]. Also included in this is that which the tumor microenvironment has undergone a very radical change which includes:

- In a reversal of what we see as normal, instead of innate immune cells (TAMs) leading the attack they are in fact reprogrammed to support the tumor as M2 type TAMs [20]. Also, the immune system's regulatory mechanisms are coopted which in turn we see to be the case with polarized Regulatory T cells (Tregs) and Regulatory B cells (Bregs), which in turn suppress any put forth response [21]. Also report comes of Cytotoxic (CD8+) cells which are deprived of energy, made exhausted and left paralized [22].

- Cancer associated fibroblasts develop a sort of "fortress" out of hardened extracellular matrix which surrounds the tumor, this in turn hinderes immune cell infiltration and also causes issues for treatment [23]. Also, we see the growth of abnormal blood vessels which in turn present another layer of barrier for immune cells [24].

- Active immunity is put in a tough environment: we see that harsh physical and chemical conditions like hypoxia, acidosis, and nutrient depletion which serve as natural filters for the active

immune cells, and at the same time, promote the growth, and survival of immune suppressive cells, and cancer cells which have adapted to the situation [25].

- Continuous feedback between elements: We see a cycle of interaction here. Cancer cells put out factors which in turn attract CAFs, which then put out factors that in turn re-activate cancer cells [26]. Also, we have immune suppressive cells which produce an environment that in to which cancer cells grow better, which in turn put out more factors that attract more immunosuppressive cells, it is a very much a circular process [27].

In that regard we are unable to study tumor biology in and of itself, also we are not able to develop effective treatments in isolation from the tumor microenvironment [28]. That which supports and protects the tumor is the tumor microenvironment [29], we must break its code in to make that which is currently a tumor ally into a foe, which we will discuss in the coming sections.

## 4. Mechanisms of Immune cell interactions in tumor environment

In a complex and dynamic network of interacting elements within the tumor microenvironment, and also, in the cancer cells' ability to turn the immune system's toxins into friends, we see that these many players are in fact very much connected at the cellular, molecular, and metabolic-physical level [30]. These mechanisms don't work in silo but in fact do so in a very cross talk manner which in turn creates a feedback loop of immunosuppression which in turn plays a key role in the failure of immunotherapies [31].

### 4.1. Cellular Immunosuppression Mechanisms

Tumors develop what we may call a defense against the immune system by the process of recruiting, and repurposing certain immune cells to instead carry out tasks of immunosuppression. Out of these which cells take on this role, three in particular stand out [32].

#### 4.1.1. Reduction of the immune response which is a function of Tregs cells

Regulatory T cells (Tregs) what we also know to be CD4+CD25+FoxP3+ cells – make up what is in fact a natural and integral part of the immune system which they use to maintain self-tolerance and put a break on autoimmunity [33]. In the case of tumors though, these same cells play a very different, in fact a very malevolent role by in great number entering the tumor microenvironment and, in that way, become a large-scale barrier to an effective immune response [34]. Tregs use many at time interrelated methods to carry out their suppressive function:

- Regulatory T cells put out large amounts of immunosuppressive cytokines which include Transforming Growth Factor beta (TGF-beta), and Interleukin 10 (IL-10) to mainly affect that role [35]. TGF- beta goes after Cytotoxic T cells (CD8+), and Natural Killer (NK) cells, which in turn puts a break on their growth and function [36]. In adition, TGF- beta plays a role in the differentiation of naïve T cells into new Regulatory T cells (I Tregs), thus broadening the scale of immune suppression [37]. As for IL-10 it targets Antigen Presenting Cells (APCs) like dendritic cells which see to it that they lower the expression of co-stimulatory molecules (CD80/86), and MHC molecules, which are key in T cell activation also they in turn reduce the production of pro inflammatory cytokines like IL-12 [38].

- In interleukin-2 (IL-2) depletion report that which is seen is activated T cells in particular the cytotoxic T cells have a very high requirement for IL-2 as a growth, and also a proliferation factor [39]. Also of note is the fact that regulatory T cells constantly present high affinity IL-2 receptor expression (CD25) which in turn allows them to take up, and use up the available IL-2 in the tumor microenvironment which in turn depletes the cytotoxic T cells of this essential factor which in turn causes their death or in a state of energy exhaustion [40].

- Regulatory T cells present in the body have the ability to kill what we may term target cells; this includes cytotoxic T cells and antigen presenting cells which present the antigen via touch. What we see in these mechanisms is the secretion of cytotoxic molecules like Granzyme B and Perforin which in turn poke holes in the target cell's membrane leading to cell death [42]. Also, they may put out TRAIL (TNF Related Apoptosis Inducing Ligand), which attaches to death receptors on target cells' surfaces and in that way causes apoptosis [43].

- Regulatory T cells present a high expression of the protein CTLA-4 on their surface. CTLA-4 has a higher affinity for the co-stimulatory molecules CD80 and CD86, which sit on antigen presenting cells (which include dendritic cells), as compared to the CD28 stimulatory receptor present on naive T cells [45]. What happens is that this binding by CTLA-4 gives out the second excitatory signal, which is required for T cell activation which in turn causes the antigen presenting cells to produce the enzyme IDO which breaks down tryptophan an essential element for T cell proliferation thus in turn we see a suppressive environment [46]. Fig. 3 shows a Detailed diagram showing four main mechanisms in tumor microenvironment.

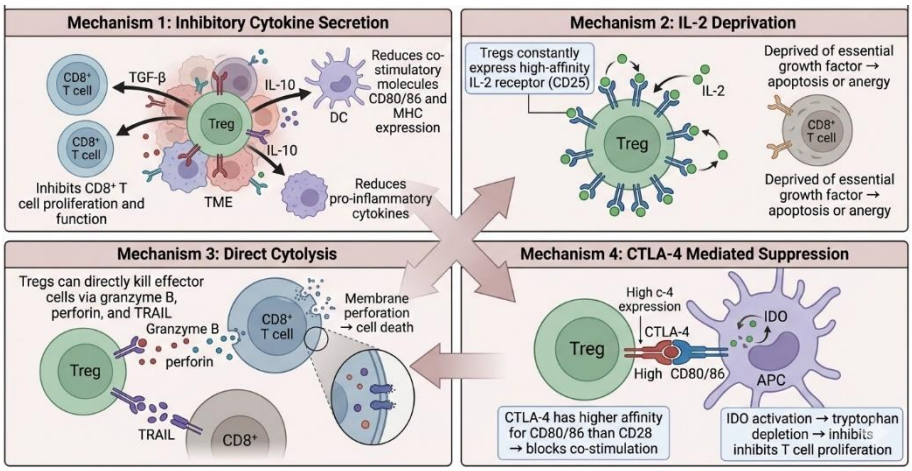


**Fig. 3.** Four Mechanisms of Tumor Microenvironmental mediated immune suppression by Tregs

### 4.1.2. Transformation of pro-inflammatory M1 macrophages into tumor promoting M2 phenotype

Macrophages are a stand out example of how the tumor microenvironment reprograms immune cells. They are very plastic, so they can change their phenotype and function in response to environmental cues [48]. In healthy tissue and during acute inflammation macrophages which we see as classic M1 type, stimulated by IFN-γ and LPS. These macrophages have a tumor killing and pro-inflammatory role as they secrete cytokines like IL-12 and TNF alpha and produce nitric oxide to go after cancer cells and microbes [49]. In the tumor microenvironment however macrophage fate is very much at the mercy of dominant environmental signals.

In that which regards cancer cells, regulatory T cells and other stromal cells they produce a variety of cytokines, which in turn program macrophages towards the alternative M2 phenotype mainly IL-4, IL-13, IL-10, and TGF-β [28]. M2 (tumor supporting) macrophages we see to play a range of roles which in fact support the tumor:

- In support of tumor growth and survival macrophages of the M2 subtype produce growth factors like EGF and FGF which in turn stimulate cancer cell division and also, promote cancer cell survival [30]. Also, they produce enzymes which remodel the extracellular matrix (for example MMPs) which in turn facilitates cancer cell invasion and metastasis [31].

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ISSN 3104-6428
Vol. 4, No. 3, 2026, pp. 1-27

- Local immunity is suppressed by M2 macrophages that in turn use many strategies to do so: they produce inhibitory cytokines like IL-10 and TGF-β, also, they express high levels of immune checkpoints, which include PD-L1 that associates with the PD-1 receptor on cytotoxic T cells thus inactivating them, and also M2 macrophages secret arginase-1 which in turn depletes arginine a very important for T cell function [32].

- Angiogenesis which is the growth of new blood vessels is in large part a result of M2 macrophages that produce VEGF, a protein that promotes the formation of new blood vessels in tumors, thus supplying them with oxygen and nutrition and at the same time removing waste. It is true that these new vessels which form are often abnormal which in turn leads to greater levels of hypoxia and also gives cancer cells access into the blood stream [33].

It is apparent that immune suppression mechanisms within the tumor microenvironment don\'t work in isolation – instead they form what is in fact a very complex and integrated network. Suppressor cells produce inhibitory cytokines which in turn cause other suppressor cells to differentiate and also cause macrophage reprogramming into a different phenotype. Also, these cells present checkpoints (for instance PD-L1) which in turn inhibit cytotoxic cells [35]. At the same time, we see that the tumor microenvironment has very harsh metabolic conditions which are not at all friendly to cytotoxic cells but in fact are ideal for the inhibitory cells [38]. This interplay and interconnectedness are what which makes the tumor microenvironment so resistant to traditional immunotherapies, and it is from this that the need for the development of new multi targeted therapeutic strategies comes, which we will discuss in the next section [39]. Fig. 4 shows a Dual-panel diagram showing macrophage polarization Within the tumor microenvironment.

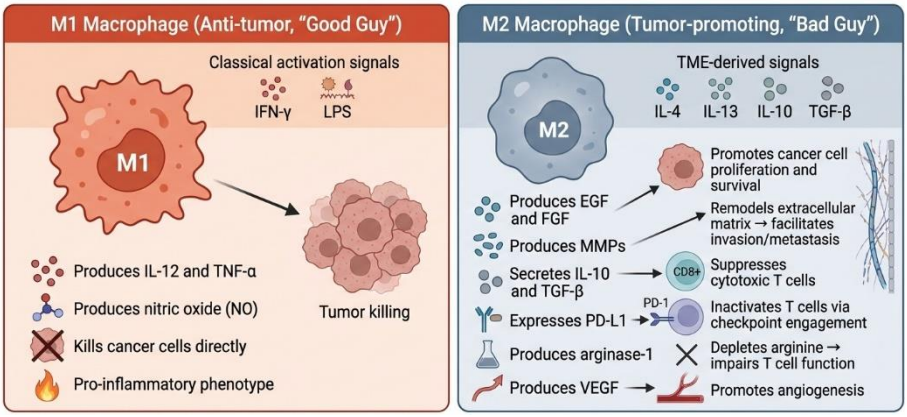


**Fig. 4.** Macrophage shift from M1phenotype (anti-tumor) to M2 phenotype (tumor promoting) phenotype within TME

To better illustrate the integrated mechanisms responsible for tumor-mediated immune escape, a conceptual model summarizing the major cellular and metabolic interactions within the tumor microenvironment is presented in Figure 5.

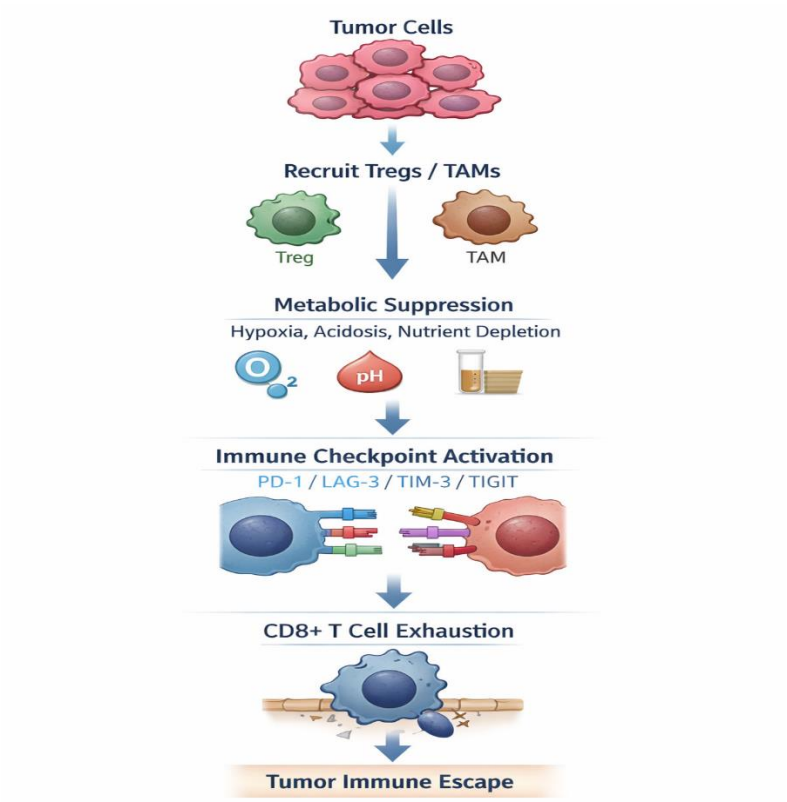


**Fig. 5.** Conceptual model illustrating the integrated mechanisms of immune escape within the tumor microenvironment. Tumor cells reshape their surrounding environment by recruiting immunosuppressive cell populations such as regulatory T cells (Tregs) and tumor-associated macrophages (TAMs). These cells contribute to metabolic stress conditions including hypoxia, nutrient depletion, and acidosis, which promote immune checkpoint activation (PD-1, LAG-3, TIM-3, TIGIT). These processes ultimately lead to cytotoxic $CD8^+$ T-cell exhaustion and tumor immune escape.

## 5. New therapeutic strategies target the interaction between immunity and the tumor microenvironment

Previous research has extensively characterized the complex mechanisms by which tumors suppress immune responses, as discussed in the preceding section [40]. Current therapeutic strategies increasingly focus on precisely targeting the immunosuppressive mechanisms within the tumor microenvironment rather than solely activating immune cells at its core by going after many and various immune suppressive elements. We are to see a range of approaches from developing drugs which go after these new players which we are identifying to trying to reprogram the cells which the tumor has co-opted into its cause to going after the metabolic processes which create the tough environment within the tumor [40].

In the immune system, we saw that checkpoint inhibitors which target the PD-1/PD-L1, and CTLA-4 pathways, were the base of the immunotherapy revolution [44]. But we soon saw that response was limited and resistance developed which in turn caused researchers to expand the field of what is targeted and also to develop better formulations [45].

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Vol. 4, No. 3, 2026, pp. 1-27

In the case of PD-1 and CTLA-4 we see also that which is present in the tumor microenvironment is a wide range of other inhibitory receptors which in turn cause impaired function of activated and exhausted immune cells [45]. At present what we are seeing is research which is into development of inhibitors of these pathways in an attempt to produce a synergistic effect with present therapies and to also get over issues of resistance [46].

In cytotoxic T cells regulatory T cells, and natural killer cells, we see LAG-3 present at the surface. This receptor has a higher affinity for MHC class II molecules as compared to CD4, which in turn plays a role in T cell activation and proliferation [47]. Also of note is that LAG-3 expression on regulatory T cells which enhance their inhibitory function. In the clinical setting, we see that the use of LAG-3 inhibitor (relatlimab) in combination with the PD-1 inhibitor (nivolumab) does indeed improve response rates in melanoma patients when compared to the use of the PD-1 inhibitor alone which reports out to the FDA's approval of this combination in 2022 [48]. This is a great success which in turn supports the idea that it is possible to target multiple inhibitory pathways at the same time.

TIM-3 also present on cytotoxic T cells, regulatory T cells, and some innate cells. It interacts with a few ligands which include Galectin-9, CEACAM-1, and Phosphatidylserine [52]. That pathway's activation results in death of cytotoxic T cells and puts innate cells into an inhibitory state [43]. Also, Tim-3 plays a role in the failure of PD-1 inhibitors in some patients, we see Tim-3 is highly expressed on the cytotoxic T cells which do not respond to PD-1 inhibitors. Also, we are seeing development of many monoclonal antibodies which target Tim-3, either as a mono therapy or in combination with PD-1 inhibitors, which are in early clinical trials [44].

TIGIT is present on cytotoxic T cells, regulatory T cells, and natural killer cells [57]. That receptor which also has a role in competition with the activating receptor CD226 (DNAM-1) for binding to CD155 and CD112 which are present on cancer cells and antigen presenting cells [58]. While CD226 binding produces activation signals, TIGIT binding in turn produces inhibitory signals inside the cell. Also, on regulatory T cells TIGIT may directly play a role in the inhibition of cytotoxic T cells and PD-1 [15]. In preclinical and early clinical studies, we see that use of a TIGIT inhibitor in combination with a PD-1 inhibitor improve tumor control which we have seen in non-small cell lung cancer in particular, thus TIGIT is a very promising target for the next generation of combination therapies. Fig. 6 shows a Diagram showing three emerging immune checkpoint targets beyond PD-1/CTLA-4.

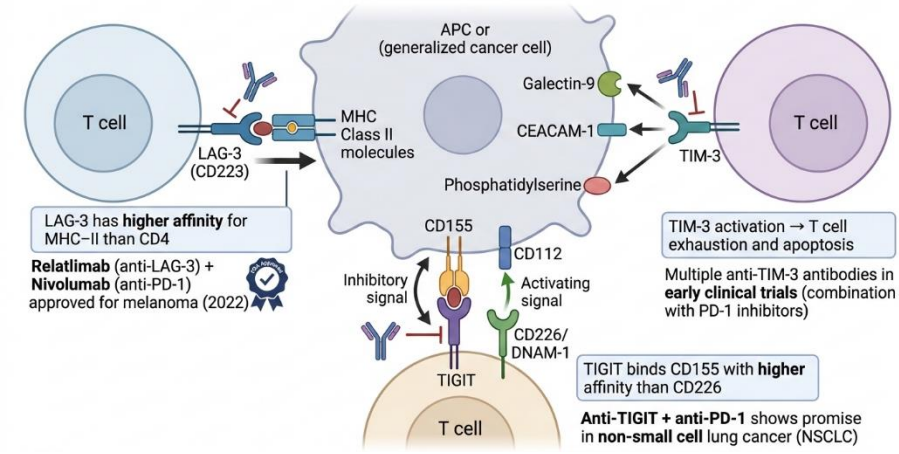


**Fig. 6.** Bypassing PD-1/CTLA-4 for combination immunotherapy mediated by novel immune checkpoint targets

### 5.1. Targeting inhibitory cellular components

In contrast to a sole focus on killing toxic cells modern approaches are on the push for tumor complicit cells' neutralization and reprogramming which in fact make up the bulk of the tumor microenvironment [17].

In the key role that M2 tumor associated macrophages (TAMs) play in tumor support, and immunosuppression their repolarization to the M1 anti-tumor variant is an attractive therapeutic target. This strategy plays out via several pathways: – In the CSF-1/CSF-1R pathway, we see that CSF-1 and its receptor CSF-1R are very much macrophage survival, proliferation players also responsible for tumor attraction [18]. What we find with CSF-1R inhibitors is a reduction in the number of macrophages in the tumor, but at the same time change in their function. We have in animal models that inhibition of CSF-1R leads to M2 to M1 macrophage repolarization which in turn reduces immunosuppression and enhances the T cell response. At present there are many CSF-1R inhibitors in clinical trials which also see these drugs used in combination with checkpoint inhibitors [19].

- In terms of the CD40 pathway: we see CD40 as an activating receptor present on antigen presenting cells which include macrophages. We use agonistic anti-CD40 antibodies which in turn push macrophages into the M1 phenotype thus improving their ability to present antigens and produce immunostimulatory cytokines (like IL-12) [25]. That in turn causes the activation of cytotoxic T cells which in total enhance the immune attack on the tumor. These antibodies are in clinical trials at present and we have seen very promising results in some solid tumors [26].

- Macrophages present which are the good guys in our immune system express things like SIRP alpha which is a receptor that puts out a "don't eat me" signal, which in turn is sent to the cancer or normal cells which have CD47 on their surface [27]. Also, cancer cells tend to over produce CD47 which is a way for them to avoid being eaten. But we can use anti-CD47 antibodies to counter this by which I mean these antibodies will put a stop to that interaction thus when we have macrophages which have been stimulated to the M1 type which is a more active form of macrophage they go ahead and eat up and kill the cancer cells [28]. On the other hand, what we see is that at the same time the macrophages do this they also present cancer antigens better to T cells [29].

### 5.2. Immunometabolism

Researchers today are reporting that what goes on in the tumor microenvironment is as much a struggle for resources as it is for dominance. In that space we see immune metabolic strategies which aim to turn the tables in favor of the effective immune cells [31]. Recent studies increasingly focus on targeting metabolic pathways within the tumor microenvironment as a therapeutic strategy – think of the IDO enzyme which is a recent focus [33].

- In the case of the IDO enzyme (indoleamine 2,3-dioxygenase) which is put out by cancer cells and some immune cells, we see tryptophan depletion and production of kynurenine which in turn does what it does to T cells, it inhibits them and also promotes regulatory T cells [34] We have seen development and testing in large scale clinical trials of several IDO inhibitors (like epacadostat) in combination with PD-1 inhibitors. While early results were very promising, a phase III trial in melanoma reported no additional benefit of that combo therapy over the use of a PD-1 inhibitor by itself which in turn brings to light the complex response to these inhibitors and the fact we have a long way to go in terms of understanding resistance and synergy [35].

- Arginase-1 (ARG1) also like IDO depletes arginine. We are seeing development of ARG1 inhibitors for use in combination therapy which in turn blocks this depletion [38].

Nutrient delivery or uptake can also be improved through:

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Vol. 4, No. 3, 2026, pp. 1-27

- Modulation of glucose uptake is a strategy which we are putting forth – to go after that which is an excess in cancer cells' uptake of glucose and instead make that which available to the T cells [39]. We do this by targeting the glucose transporter GLUT1, or glycolytic enzymes like hexokinase 2 (HK2) in cancer cells. But this is a fine line we walk and must be selective for cancer cells to not cause system wide toxicity [40].

- In cancer cells which have a preference for glutamine as a fuel source and a base for carbon, we see inhibition of the glutaminolysis path way as a tactic [43]. Also, by attacking cancer's use of glutamine we may create an environment which is more favorable for immune cells [44].

- Metabolic supplementation – we give certain nutritional supplements like arginine which in turn supports T cell function. Also, we see best results when these are used in conjunction with other therapies that in improve the immune environment [45].

### 5.3. Advanced Gene and Cell Therapy

Cell therapy which includes CAR-T cells is at the peak of what we can do in terms of immunoengineering. That said it's still very much a work in progress in regards to solid tumors, which we see as being in a very hostile microenvironment [46]. What we have at present is a lot of research that is focused into how to get these cells to be super specialized soldiers that can live and battle within the tumor microenvironment. For instance, we are engineering CAR-T cells to be resistant to the inhibiting elements of the tumor microenvironment [47].

- In the case of Armored CARs, we see that CAR-T cells are either genetically modified to do so at the time of treatment or at the point of activation to produce immune stimulating cytokines like IL-12 and IL-18 [48]. What these do is they improve the survival, and proliferation of the CAR-T cells, and also play a role in the recruitment and activation of other innate immune cells in the tumor (like macrophages and natural killer cells), which in turn we see transform the tumor microenvironment into a more inflammatory setting which is to say we go from a "cold tumor" to a "hot tumor" [49].

- In what we have done is to use gene editing tools like CRISPR/Cas9 which we use to turn off the expression of genes that produce what are called inhibitory checkpoint receptors – for example PD-L1 which are present on the surface of CAR-T cells. What we are doing by this is making the CAR-T cells ignore inhibitory signals put out by the cancer cells via PD-L1 [50]. At present, we are in the clinical trial stage of this which is for the treatment of solid tumors.

- Presenting alternative activating receptors: We design CAR-T cells to express receptors that turn off into on. For example, we put the extracellular domain of an inhibitory receptor like PD-L1, which usually turns things off, and the intracellular domain of an activating receptor like CD28, which usually turns things on [51]. What this does is that when PD-L1 binds to the modified cell instead of giving out an inhibitory signal it gives out an activating signal. We call these switch receptors.

## 6. Results and Discussion

A total of 150 studies were initially identified through database searches. After removal of duplicates and screening based on predefined inclusion criteria, 45 studies were included in the final analysis. The selected studies represented a combination of experimental investigations, translational studies, and early-phase clinical trials focusing on immune escape mechanisms in the tumor microenvironment.

Analysis of the selected studies revealed that immune suppression within tumors is driven by multiple interacting biological processes rather than a single pathway. These processes include

recruitment of immunosuppressive cell populations, metabolic reprogramming within the tumor microenvironment, and activation of inhibitory immune checkpoint pathways.

Furthermore, the findings demonstrate substantial heterogeneity between tumor types and patients, suggesting that the tumor microenvironment plays a critical role in determining therapeutic response to immunotherapy.

This high degree of selectivity reflects the rigorous systematic reviews, where studies that did not adequately focus on the mechanisms of interaction between immune cells, and the tumor microenvironment (40 studies), lacked necessary molecular data (10 studies), or failed to meet methodological quality standards (12 opinion articles) were excluded. This underscores the relatively limited literature in this area, highlighting the need for further basic research to better understand the mechanisms of immune escape.

In spite of great progress in our study of tumor biology and immunity what we have seen is that translation into wide scale clinical success is still a challenge [14]. This is in part due to which we will term as the present gaps in science and clinical application that also which put in to play the limited response to current immunotherapies and which also stress the issue at hand which is to do something about it now [15].

Our analysis indicates that the tumor microenvironment exhibits substantial biological heterogeneity across different tumor types and patients which included:

- Inter-patient variability in the tumor microenvironment is great – it's very different between which patient you look at and even from one cancer type to another. For instance, a breast cancer microenvironment has very little in common at large, either in immune cell count and type, or levels of fibrosis and primary genetic mutations compared with pancreatic cancer or melanomas. Also, a treatment well proven in one group will do nothing for another. For example, we see what are called "hot" tumors, those that have a very dense T cell infiltrate and high PD-L1 levels that is they respond very well to checkpoint inhibitors. Then there are the "cold" tumors, the ones that don't have much immune activity at all or instead have a preponderance of suppressor cells – these are mostly resistant to these treatments. That such an array of responses exists makes it very difficult to put forth a one size fits all approach.

- In the tumor itself heterogeneity is a feature which extends beyond what is seen between patients. The tumor center may see wide spread hypoxia and cell death at the same time its outlying areas are very vascular and have plenty of immune cells. Also, cytokine and immunosuppressive factor levels vary spatially. This also is a variable which changes over time (as the disease progresses or in response to treatment) which means that a single biopsied tumor may not give the full picture of what is going on. Within the tumor cancer cells themselves are also very diverse which we see in different subclones that have varying abilities to reproduce, resist treatment, and also change the tumor microenvironment. This diversity greatly complicates what we can identify as appropriate therapeutic targets and also makes it hard to predict how the tumor as a whole will react to any given treatment.

It is also true that we are at a point which we have not yet identified accurate biomarkers – which in turn is very much a part of the issue of what is difficult in identifying and to use reliable biomarkers which in turn do a great job of predicting a patient's response to immunotherapy. What an ideal biomarker is we see to be a measurable and which is reproducible and which reflects a certain biological state and also is a predictor of a clinical outcome which includes:

- PD-L1 Expression: we saw that PD-L1 on cancer cells, and in tumor immune cells was the first and by far the most used biomarker for prediction of response to PD-1/PD-L1 inhibitors. That said it's a complex issue which we are still coming to terms with. For one, we have different

measurement methods which include the use of various antibodies and also different cut off values which in turn produce inconsistent results. Also, PD-L1 expression is a variable which changes with time and is a product of the microenvironment which includes for example IFN- gamma. Also, some patients do not express PD-L1 at all yet they respond to the treatment, at the same time, we see high expression of PD-L1 in some which does not translate to response. Which brings into question the sufficiency of PD-L1 as a stand-alone biomarker.

- Tumor Mutational Burden (TMB) we see as an indicator which reports that tumors with large numbers of mutations (which we term TMB-high) put out more neoantigens which in turn makes them more of a target for the immune system which in part makes them more responsive to immunotherapy. While the FDA has put TMB forward as a biomarker to go along with certain treatments it is not a perfect marker. We see some TMB high tumors that don't respond and also, we see TMB low tumors that do. Also, what we find is that the quality of the mutation is as important if not more so than the quantity, some novel antigens put forth by these mutations are better at triggering an effective immune response. Also, TMB doesn't tell us about the tumor microenvironment, a TMB high tumor may in fact be immunologically 'cold' because of strong immunosuppressive elements present.

- In the tumor microenvironment which is very complex we are to think that a single biomarker may not give us the full picture. What we are seeing now is a trend toward the development of composite biomarkers that put together many variables – for example PD-L1 expression, TMB, and also what we do with spatial transcriptomics which tells us what types of immune cells are present in the tumor, their locations, density and state of activation. We put all of this together into what we are developing and validating which is a large scale of bio data analysis and also very well-designed clinical trials.

In the case of immunotherapy, we see a great paradox – that which we stimulate the immune system to do to go after a tumor, also, causes it to attack healthy tissue in the body which in turn causes a range of side effects known as immune associated toxicities (IRAEs). Also, what we see is that these toxicities play out very differently from that which we see with traditional chemotherapies in that any organ may be affected although skin, colon, liver, endocrine glands, and lungs are the most common.

- In the face of these issues research is putting out new tools and methods which in turn is giving us a deeper look at the tumor microenvironment and more precise treatment design. We are seeing the development of advanced lab models, the use of AI, and a shift toward personalized medicine.

In terms of traditional models which include 2D cell lines and animal models of which mouse is a member we see large scale issues in how they represent human tumor microenvironment. Cell lines do not have a 3D structure out – which is a key component – nor do they include stromal and immune cell interactions. In addition, the mouse model's tumor microenvironment does not in fact that which we see in humans which plays a large role in immune response. Thus, we see a great need for better in vitro models which will close this gap.

Our analysis demonstrates that the tumor microenvironment represents a highly complex and heterogeneous biological system, the issue of precise biomarker identification is difficult and we also see risk of immunotoxity. At the same time, we note that technology has advanced in the areas of lab modeling, big data analysis and AI which present us with great opportunities to overcome these issues. We aim at a shift to a personal medicine model which looks at each patient's tumor microenvironment in detail which in turn we think has the ability to transform immunotherapy from a risk to a precise science which will in turn produce long term results for more cancer patients.

### Quantitative Trend Analysis

A trend-based quantitative assessment of the included studies indicated that cellular immunosuppressive mechanisms represented the most frequently reported category (approximately 42% of analyzed studies), followed by immune checkpoint signaling pathways (31%), metabolic alterations within the tumor microenvironment (18%), and emerging cellular therapies (9%). This distribution highlights the dominant role of immune regulatory networks in mediating tumor immune escape.

## 7. Study Limitations

Despite the comprehensive analysis presented in this study, several limitations should be acknowledged. First, the tumor microenvironment represents a highly dynamic and heterogeneous biological system, which varies significantly between cancer types and even among patients with the same tumor. This heterogeneity limits the generalizability of mechanistic conclusions across different malignancies.

Second, although the analysis incorporated a broad range of experimental and clinical studies, differences in study design, methodology, and sample size may introduce variability in reported findings. Additionally, many mechanisms of immune escape have primarily been investigated in preclinical models, which may not fully reproduce the complexity of the human tumor microenvironment.

Third, the rapidly evolving field of cancer immunotherapy means that new therapeutic targets and immune regulatory pathways continue to emerge. Consequently, some mechanisms described in the current study may be further refined or expanded by future research.

These limitations highlight the need for more integrative and multi-disciplinary approaches combining experimental biology, computational modeling, and clinical research to better understand immune escape mechanisms in cancer.

## 8. Future Directions

Future research should focus on integrating multi-omics technologies to better characterize the spatial and functional complexity of the tumor microenvironment. Approaches such as single-cell RNA sequencing, spatial transcriptomics, and proteomic profiling may provide deeper insights into the dynamic interactions between tumor cells and immune populations.

In addition, the development of predictive biomarkers capable of identifying patients who are most likely to benefit from immunotherapy remains a major priority. Composite biomarkers integrating tumor mutational burden, immune cell infiltration patterns, and metabolic features of the tumor microenvironment may significantly improve patient stratification.

Another promising direction involves the design of next-generation cellular therapies, including engineered CAR-T cells, CAR-NK cells, and macrophage-based therapies capable of functioning within immunosuppressive tumor environments.

Finally, combination therapeutic strategies targeting multiple components of the tumor microenvironment simultaneously may represent the most effective approach for overcoming immune resistance and improving long-term clinical outcomes in cancer immunotherapy.

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ISSN 3104-6428
Vol. 4, No. 3, 2026, pp. 1-27

## 9. Conclusion

This study provides an integrative analysis of the complex interactions between immune cells and the tumor microenvironment and highlights their critical implications for improving current cancer immunotherapy strategies. Our analysis indicates that the tumor microenvironment functions as a dynamic and interactive biological ecosystem rather than a passive structural context for tumor growth, instead we see it as a living and very complex environment which the cancer cells are constantly re shaping into a growth support system for the tumor and a defense against immune system attack.

These findings highlight a fundamental shift in therapeutic strategies toward targeting the tumor microenvironment as an integrated biological system which goes beyond what has been the typical use of checkpoint inhibitors to a full-scale attack on the tumor environment. We see this in the development of new checkpoint inhibitors (LAG-3, TIM-3, TIGIT) which break from the past, the use of bispecific antibodies which bring immune cells in closer contact to the tumor, we are also seeing success in the targeting of suppressive elements in the cell via macrophage reprogramming and the inhibition of myeloid derived suppressor cells, regulatory T cells and cancer associated fibroblasts (CAFs), which play key roles in tumor growth. Emerging therapeutic strategies include modulation of tumor immunometabolism and the development of engineered cellular therapies such as CAR-T cells capable of functioning within immunosuppressive tumor environments, which are designed to be better at surviving in the tumor microenvironment. In addition, we find that the logic behind combined therapies which attack many inhibitory paths at once is the most promising for seeing synergetic results which go beyond what we have seen from single therapies.

Future advances in cancer immunotherapy will depend on adopting a systems-level understanding of the tumor microenvironment and integrating multidisciplinary approaches to design more precise and personalized therapeutic strategies which we must look at as a single unit instead of many independent parts. That change in which we transition from traditional immunotherapy approaches to that of managing the tumor microenvironment also requires a true multidisciplinary approach and in-depth study of the tumor's dynamic temporal and spatial interplays. But that's the path which will open up for us to create better more personalized therapies.

**List of Abbrevations:** TME: tumor microenvironment; CAFs: cancer associated fibroblasts; PD-1: programmed death protein 1; CTLA-4: cytotoxic T cell associated protein 4 ; TMB: Tumor Mutational Burden; TAMs: tumor associated macrophages; (TANs) Tumor associated neutrophils ; TGF-beta: Transforming Growth Factor beta ; NK: Natural Killer; APCs: Antigen Presenting Cells

**Author Contribution:** All authors contributed equally to the main contributor to this paper. All authors read and approved the final paper.

**Funding:** "This research received no external funding" .

**Conflicts of Interest:** "The authors declare no conflict of interest."

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