Cancer Immunotherapy: Advances, Challenges, and Future Directions

Nesrin Ibrahim Tarbiah, PhD*

ABSTRACT

Cancer immunotherapy represents a novel approach that harnesses the immune system to recognise and eliminate malignant cells. Physician must be well versed in this field, not only in treating cancer itself, but also in manging immune system-related complications. An additional crucial focus of cancer research is understanding how the tumour microenvironment (TME) regulates the rates of tumour growth and metastasis, so that parallel tests and proper treatments can be accordingly developed. The presence of TME, together with its immune cells infiltrating the tumours, crucially influences the outcome of immunotherapy by sometimes converting the anti-tumour response into a pro-tumour type. Mass cytometry and single-cell analysis approaches have facilitated our understanding of TME by demonstrating the variety of immune cells which might be potential targets of treatment. This review covers various types of immunotherapies, including immune checkpoint inhibitors (ICIs), Adoptive cell transfer (ACT) and oncolytic viral therapies. In addition, it discusses novel strategies targeting the TME that hold promise for improving outcomes in cancer immunotherapy.

Keywords: cancer immunotherapy, tumour microenvironment, immune checkpoint inhibitors, CAR-NK and CAR-Tcell.

INTRODUCTION

Cancer management has long posed a significant therapeutic challenge, owing to the limitations of conventional treatments such as surgery, chemotherapy, and radiotherapy[1]. These conventional treatments associated with toxic side effects and inability to prevent recurrence and metastatic growth of tumours. Under normal physiological conditions, the immune system plays an important role in the recognition and destruction of abnormal or malignant cells as a natural defence mechanism from tumorigenesis[2].

Cancer immunotherapy, hence, is a promising therapeutic solution. In cancer immunotherapy, the immune system of the patient is activated to identify and eliminate cancer cells through different modern approaches. Such methods may involve targeted therapy either directly against tumour cells or non-specifically enhancing immune effector mechanisms to foster the antitumor response[3]. The key aspect about immunotherapy is that it's an immunologically active therapy that promotes the generation of memory CD8+ T cells; their presence thus confers the long-term anti-metastatic protection against any patient relapse[4].

Apart from the huge therapeutic promise, it is still a developing area, with many questions on the scientific and clinical front still awaiting answers. With continuous advancement in immunological research and technological advancement, it is only expected to improve integration into standard oncological care[5]. A deeper understanding of the barriers preventing current cancer immunotherapy, particularly cellular plasticity, complexity, and the antagonism of the tumour microenvironment (TME), which consists of numerous tumours, immune cells, blood vessels, and metabolic components, is agonized to improving the practical efficacies of onco-immunology-based therapies.

TME places a heavy burden on the planning of patient's treatment. TMEs influence the effectiveness of treatment strategies and tumorigenesis. The enhancement of immune response to fight tumours hence aiding in effective cancer treatment is accomplished by putting attention on the TME[6]. The TME is a complex system containing numerous growth factors that direct many biological processes in the tumour itself and thus have a strong influence on immunotherapy for cancer. Another reported application of biomaterials is their use in targeting the tumour microenvironment for improved immunotherapeutic efficacy[7].

In order to avoid immune-mediated destruction, tumour cells utilize immune checkpoints or recruit suppressive cellular components in the TME[8]. An approach that has received much attention in the development of next-generation cancer therapies is forcing the immune system to target into tumours[9]. The spectrum of cancer immunotherapies has been developed to suppress the mechanisms of tumour immune evasion and to stimulate the immune system toward antitumor activity. This review considered the main types of cancer immunotherapy: immunomodulators, immune checkpoint inhibitors (ICIs), adoptive cell-based therapies like CAR-T and CARA-NK therapies, and oncolytic virus therapy.

The Tumour Microenvironment

The tumour microenvironment is a dynamic and multifactorial ecosystem onto which the genesis of the tumour, immune evasion, and resistance to therapies take place. It contains malignant cells and various other components such as fibroblasts, endothelial cells, extracellular matrix elements, and immune cells as well. Such a complex network generates an ever-evolving milieu filled with pro-tumorigenic and anti-tumorigenic factors that steer cancer in each direction[10].

Infiltration of immune cells within the TME is key in modulating antitumor and protumour responses. Certain effector populations, including $CD8^+$ cytotoxic T lymphocytes, $CD4^+$ helper T1 (Th1) cells, natural killer (NK) cells, dendritic cells (DCs), and M1 macrophages, are involved in tumour suppression via cytokine release (e.g., IFN-γ), antigen presentation, and killing[11]. On the other hand, immunosuppressive subtypes like regulatory T cells (Tregs), Th2 cells,

* Biochemistry Department, Faculty of Science
King Abdulaziz University, Jeddah, Saudi Arabia.
Email: ntarabah@kau.edu.sa

M2 macrophages, and myeloid-derived suppressor cells (MDSCs) promote the tumour by inhibiting immune surveillance and creating an immunosuppressive TME[12].

Chemokines play crucial roles in shaping how immune cells are recruited and distributed spatially within the TME. For instance, CX3CL1 assists in the migration of $CD8^+$ cytotoxic and memory T cells, thereby empowering the antitumor effect[3]. In contrast, suppressive chemokines such as CCL19 and IL-16 recruit and activate Tregs that escalate immune evasion mechanisms. MDSCs are often expanded under malignant setting and greatly inhibit the activities of effector immune cells that contribute to tumour advancement and resistance against therapies.

Immune cells performing dual function in tumour biology as shown in Figure 1: On another side, immune suppressive cells such as Th2 cells, regulatory T cells (Tregs), M2 macrophages, myeloid-derived suppressor cells (MDSCs), and DC-2 support tumour advancement by releasing IL-10, TGF-b, and other immunosuppressive factors[13].

The spatial distribution of immune infiltrates, along with the intermixed cellular diversity in the tumour microenvironment, determines the clinical outcome. Immune cells are differently localized in discrete tumour areas-the invasive margin, tumour core, and tertiary lymphoid structures (TLSs). These TLSs, which resemble secondary lymphoid organs, are often situated near high endothelial venules (HEVs) that facilitate immune surveillance and the recruitment of lymphocytes from circulation. Elevated densities of $CD8^+$ cytotoxic T cells and memory T cells within these compartments are generally correlated with improved prognosis and enhanced responsiveness to immunotherapeutic interventions[14].

Angiogenesis is also an important part of TME biology. Tumour-induced neovascularisation ensures a supply of nutrients and oxygen while simultaneously deterring effective immune cell infiltration. The abnormal structure and function of tumour-associated vasculature often led to hypoxia, thereby biasing the immune response towards suppression and promoting tumour growth[15].

Figure 2 showed how Fibroblasts are transformed into cancer-associated fibroblasts (CAFs) under the influence of TGF-β. Epithelial cancer cells adopt a migratory mesenchymal phenotype in response to IL-1β, IL-6, and TNF-α, contributing to tumour invasion. VEGF promotes angiogenesis by converting normal vasculature into abnormal tumour vessels. The illustration highlights how various cytokines (e.g., IL-10, IL-35, MCSF-10, TGF-β, VEGF) modulate immune suppression and cell recruitment (fibroblasts, endothelial cells), driving tumour progression.

Recently, single-cell techniques have advanced considerably with mass cytometry, scRNA-seq, and spatial transcriptomics being at the forefront. These technologies help study the complexities of cellular and molecular compositions of the TME as well as how TME dynamics respond to ICI-based treatment[16]. The emergence of these technologies, through which unusual immune-subsets and phenotypic deviations of T cells, macrophages, and other stromal components were detected, which has shed light on potential key players in immune dysfunction and therapeutic resistance[17]. For example, scRNA-seq established unequivocal evidence for the presence of various populations of functionally heterogeneous T cells undergoing diverse states of exhaustion, which could probably respond differently to checkpoint blockade therapies[18].

Spatial-functional analysis further delineates immune-cell plasticity and adaptability within tumours. The functional states of tumour-infiltrating lymphocytes, including cytotoxicity and cytokine production, are affected by complex interactions with their environment. Therefore, a possible approach to improve cancer immunotherapy could be the alteration of such interactions, either by reducing the suppressive cells such as Tregs and MDSCs or by promoting the ability of $CD8^+$ T cells[19].

While the tumour vasculature and the stromal compartment were extensively investigated, advance immunotherapies such as immune checkpoint inhibitors, adoptive T cell transfer, CAR T-cell therapy, and cancer vaccines were developed. Immunotherapies targeting the TME seek to reprogram it to generate antitumor immune responses or activate tumour-protective mechanisms. Thus, TME-targeting therapies are potential adjuncts to other cancer immunotherapeutic approaches for enhancing the potency and duration of antitumor responses. In contrast, immunosuppression causes tumor progression as the immune system opposes tumorigenesis[20]. A better understanding of the contributions and interactions between innate/adaptive immune cells in the TME must be deeply investigated to fully grasp the immunotherapeutic mechanisms, , that help in developing predictive biomarkers and new therapeutic targets[21].

IMMUNOTHERAPIES

Adoptive cell transfer (ACT) therapy

Within this kind of immunotherapy, the adoptive cell transfer involves the infusion of lymphocytes-an autologous type, or one that is genetically engineered to enhance the antitumor immune response of a host. These transferred cells are considered living drugs and can undergo expansion inside the host body and specifically attack tumour cells that express their cognate antigens[22]. ACTs have been among the most successful treatments against cancer using cells that may be genetically modified: transgenic TCR lymphocytes, or tumour-infiltrating lymphocytes (TILs). However, an overwhelming majority of patients fail to respond to these treatments or at best develop a temporary response, since cancer cells can induce mechanisms to confer an immunological evasion against them. Researchers identified that the larger group of patients with common epithelial cancers contains immune cells targeting the proteins formed by their mutagenic cancers, igniting efforts to past-adoptive cell transfer immunotherapy for these patients[23]. At present, two classes of genetically altered T cells, namely chimeric antigen receptor (CAR) T cells and T-cell receptor (TCR)-engineered T cells, have been created for adoptive transfer and have had major successes in attacking malignant tumours. CAR-T cell and CAR-NK will be discussed in detail latter in this review.

Chimeric antigen receptor technology has been an important advancement in cancer treatment, particularly for adoptive immunotherapies. Chimeric antigen receptors are fusion proteins. They have an extracellular antigen-binding domain, which most commonly comprises single-chain variable fragments (scFv), and intracellular signalling domains that activate immune effector functions. The first-generation CARs had only the CD3ζ signalling domain. Later generations saw the addition of the co-stimulation molecules CD28, 4-1BB (CD137), OX40 (CD134), and ICOS, greatly enhancing the proliferation, persistence, and cytotoxicity of T cells[10]. Further enhancing this platform, fourth-generation CARs or 'armoured CARs' gene-engineer T cells to secrete immunomodulatory cytokines in response to the TME, which greatly amplifies antitumor immunity[24].

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors have greatly impacted the field of cancer therapy, especially with melanoma, non-small cell lung cancer, renal cell carcinoma, and many others. The drugs interrupt the body's

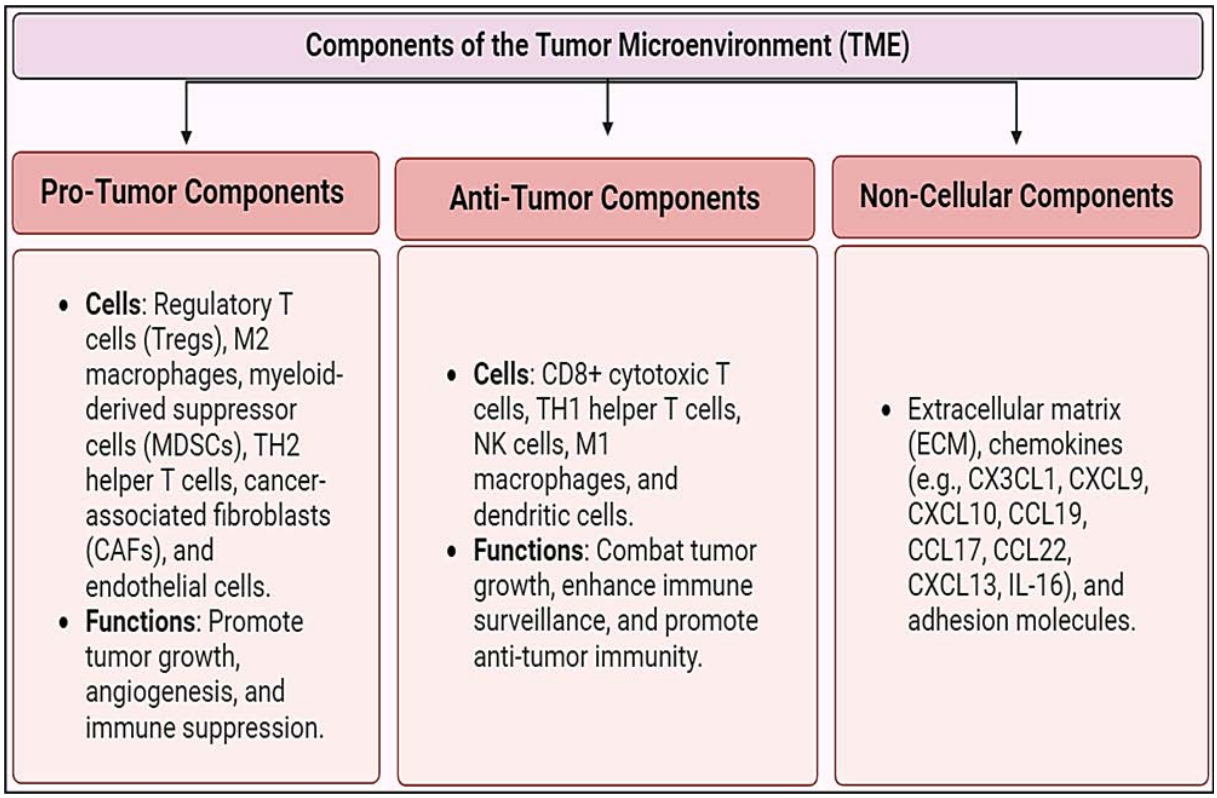

Figure 1. Immune Modulation Within the Tumour Microenvironment (TME)[13].

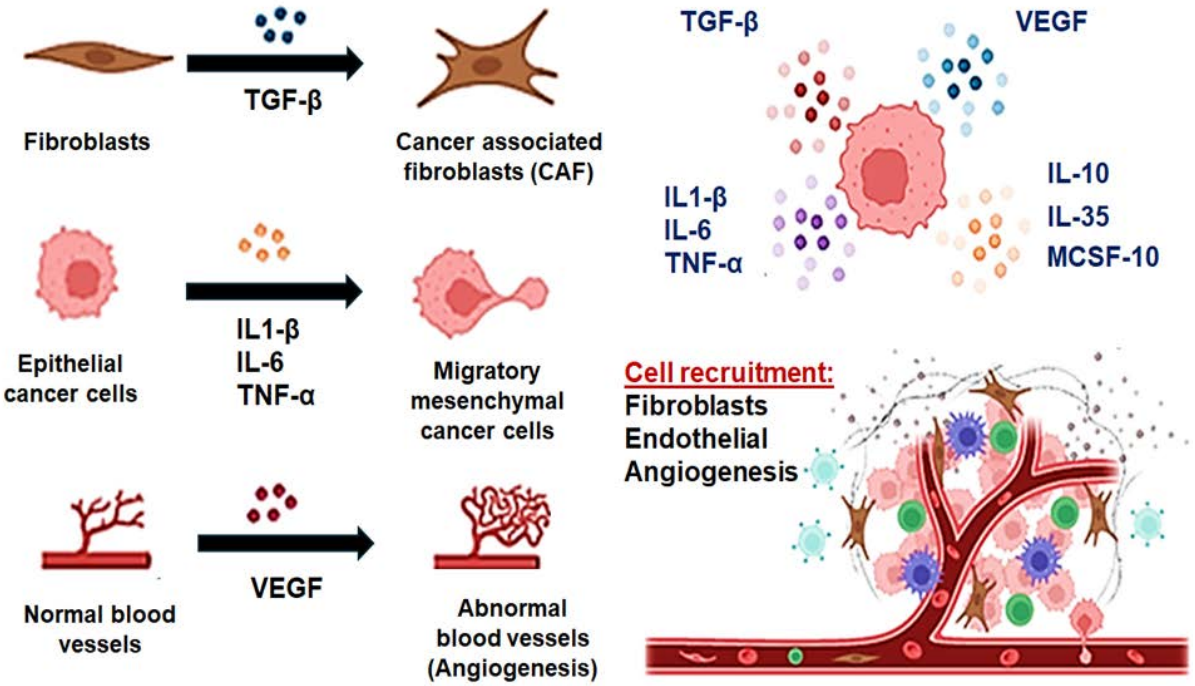

Figure 2. The Role of Cellular Interactions in Tumour Microenvironment Remodelling[10].

regulatory systems that usually keep the immune system check, but the tumours utilize their systems to evade immune attack. These substances are intended to mainly block three molecules: cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), or its ligand PD-L1. Anti-CTLA-4 antibodies (e.g., ipilimumab) and anti-PD-1 antibodies (e.g., nivolumab and pembrolizumab) constitute two major classes of immune checkpoint inhibitors currently used in clinical practice. These agents have been authorized by the US Food and Drug Administration (FDA) for the treatment of different types of malignancies. Additionally, some anti-PD-L1 antibodies, namely durvalumab, avelumab, and atezolizumab, are currently being used clinically or are in an advanced stage of development[25].

Cytotoxic T-lymphocyte-associated protein 4, shares an evolutionary homology with the co-stimulatory receptor CD28, is an inhibitory receptor expressed on T cells and turns off T cell activation. While in T cell priming, CD28 binds to the B7 molecules-CD80 or CD86-on the surface of antigen-presenting cells in order to deliver a co-stimulatory signal required for T cell activation, CTLA-4 with its higher affinity for B7 ligands competes with CD28 and suppresses co-stimulatory signalling vital for the complete activation of T cells[26]. Blocking CTLA-4 with monoclonal antibodies could induce potent antitumor immune responses leading to tumour regression in early days, thus laying the basis of checkpoint blockade immunotherapy[27]. Ipilimumab was the first ICI to be approved in cancer therapy, and the first monoclonal antibody against CTLA-4 because of its effects in sustaining durable T cell activation and clinical responses[28].

PD-1, on the other hand, is a negative regulator expressed on activated T cells. Its ligands are variously induced on cells of hematopoietic and non-hematopoietic origin, including tumour cells, to suppress the immune reaction for the purpose of pre-empting autoimmune responses and maintaining lateral tolerance. However, PD-L1 is expressed in a wide variety of hematopoietic and non-hematopoietic cells, whereas that of PD-L2 is largely restricted to dendritic cells and macrophages[29]. Tumours exploit this pathway by overexpressing PD-L1, which binds to the PD-1 receptor on tumour-infiltrating lymphocytes (TILs), thereby inhibiting the effector function of T cells and causing immune escape. Therapeutic antibodies that block the PD-1/PD-L1 axis clear the way for T-cell activation and, subsequently, for antitumor immune responses[30]. In addition, a good body of evidence indicates that signalling through PD-1/PD-L1 promotes regulatory T cell (Treg) stability and function, and its blockade could dampen Treg-mediated immunosuppression within the tumour microenvironment[31].

Mechanistically, each immunotherapy helps at so-called different stages of immunogenicity. CTLA-4 blockade enhances T-cell priming in the lymphatic organs, while PD-1 inhibition restores T-cell effector function in the TME [9]. Under broad immunomodulatory effects, CTLA-4 inhibitors may cause a higher than usual frequency of immune-related adverse events[32].

There has been an active interest in continuing to find more reliable prognostic biomarkers such as PD-L1 expression, tumour mutational burden, and TLSs, but none of these really works all the time. Mechanisms of resistance include loss of antigen presentation, upregulation of alternative immune checkpoints like LAG-3, TIM-3, and TIGIT; exclusion, inactivation, or dysfunction of the effector cells; and accumulation of suppressive myeloid or stromal components[33].

Immune checkpoint inhibitors (ICIs) provide critically important treatment vantage points in cancer care while a whole host of side effects—immune-related adverse events (irAEs)—may be caused by using them. These toxicities arise from the nonspecific activation of the immune system and can almost affect every single organ system. It is imperative to recognize that anti-CTLA-4 drugs tend to cause irAEs more than do anti-PD-1/PD-L1 drugs. Hypothesizing behind this observation, the investigators suggest that CTLA-4 inhibitors stop T cell activation at the very early priming phase; hence, a heightened systemic immune response is instigated.

Immune checkpoint inhibitors are associated with a distinctive set of adverse events known as irAEs, which result from immune activation against normal tissues. The most reported irAEs are cutaneous in nature and consist of rashes, gastrointestinal toxicities including colitis, hepatotoxicity, and a wide variety of endocrine disorders-from hypothyroidism to adrenal insufficiency to hormone deficiencies induced by hypophysitis[34]. In pooled analysis of 576 patients with melanoma on nivolumab, dermatologic toxicities tended to manifest early with median onset at around 5 weeks, whereas renal complications came in late around 15 weeks after initiation of treatment[35].

The management of irAEs depends greatly on their severity. Mild-to-moderate toxicities usually require just a temporary halt of immunotherapy. Severe irAEs (grade ≥3) basically call for systemic corticosteroids to be given as immunosuppressors at 1–2 mg/kg prednisone equivalent dose while the treatment is interrupted[36]. Other immunosuppressive agents may be employed when steroids are ineffective. Infliximab is commonly administered for resistant immune-mediated colitis, whereas mycophenolate mofetil is the preferred option in autoimmune hepatitis, where infliximab is contraindicated. Hepatic toxicities may resolve within approximately three weeks, while dermatologic adverse events can persist for as long as 29 weeks[37].

There are some concerns that the immunosuppressive management of irAEs, particularly with corticosteroids, may interfere with the antitumor activity of ICIs. Emerging data, however, suggests the opposite. A retrospective analysis of 298 patients treated with ipilimumab showed that 85% had irAEs, of whom 35% required corticosteroids and 10% anti-TNF treatment. No significant difference in the survival rate or treatment-effect differences were observed in patients receiving, or not receiving, immunosuppressive therapies[38]. Correspondingly, pooled investigations among nivolumab-treated study groups revealed the absence of any detrimental impact on response rates or duration of response exerted by immunosuppressive interventions[35].

The findings, therefore, support the idea that irAEs can be managed effectively with immunosuppressive agents without affecting the clinical benefits of ICIs. Nevertheless, timely diagnosis and appropriate treatment are the mainstay for both patient safety and continuation of treatment. From clinical perspective, ICIs have been proven to be quite effective against a variety of malignancies and especially those with high tumour mutational burden as these are likely to produce immunogenic neoantigens that can evoke more vigorous immune response[39].

Immune Cells and Tumour Immunity

A complicated balance occurs between tumour suppression and tumour progression by various immune populations in the TME. The immune types that mediate tumour suppression are the M1-polarized macrophages, Natural Killer (NK) cells, NKT cells, T helper 1 (Th1) cells, $CD8^+$ cytotoxic T cells, Th17 cells, T follicular helper (Tfh) cells, dendritic cells type 1 (DC-1), and B cells producing tumour-specific immunoglobulins. The effector coursing cells perform antitumor functions by mechanisms such as the secretion of proinflammatory cytokines, interferon-gamma (IFN-γ) and interleukin-21 (IL-21), direct cytotoxicity, and presentation of tumour antigens.

In contrast, the immune cells that tend to promote tumour progression include M2 macrophages, Th2 cells, T regulatory cells (Tregs), myeloid-derived suppressor cells (MDSCs), DC-2 cells, and N2 neutrophils. These immunosuppressive cells secrete inhibitory cytokines such as IL-10 and transforming growth factor-beta (TGFβ) that exert their suppressive effect on antitumor immunity, support immune evasion, and stimulate tumour growth and development[40] (Figure 3).

This illustration highlights the opposing roles of immune cells in modulating tumour development. Tumour-suppressive cells are depicted on the left, whereas tumour-promoting cells are illustrated on the right[41].

Furthermore, immune cell composition significantly impacts therapeutic responses. As shown in Figure 4, the TME of non-responders is enriched with regulatory T cells (Tregs), exhausted $CD8^+$ T cells, M2-like macrophages, immunosuppressive dendritic cells (DCs), and cancer-associated fibroblasts (CAFs), which collectively contribute to immune evasion and treatment resistance. In contrast, responders exhibit a TME enriched with functional $CD8^+$ and $CD4^+$ T cells, M1-like macrophages, $CXCL9^+$ and $CXCL13^+$ dendritic cells, and elevated expression of transcription factors such as TCF7, supporting effective antitumor immunity and therapeutic efficacy.

This figure contrasts immune infiltration patterns between therapy responders and non-responders. Immune activation and tumour clearance are enhanced in responders, while immunosuppression and tumour persistence dominate in non-responders[42].

T cells and tumour immunity

Emerging immunotherapeutic strategies that harness T cells to target malignant cells are gaining significant momentum. T cells play a central role in antitumor immunity and rely on the Major Histocompatibility Complex (MHC) for antigen recognition and activation (Figure 5). MHC molecules are essential for enabling TCRs to detect tumour-associated antigens. MHC class I molecules, expressed on all nucleated cells, present antigens to cytotoxic T lymphocytes ($CD8^+$ T cells), whereas MHC class II molecules are restricted to professional antigen-presenting cells (APCs) and are involved in the activation of helper T cells ($CD4^+$ T cells). Effective T cell activation also requires costimulatory signals, notably the interaction between CD28 on T cells and B7 molecules on APCs, in addition to TCR-MHC engagement[43].

T-cell receptor diversity generated by somatic gene rearrangement is a technology that grants T-cell recognition of tumour-specific antigens[45].

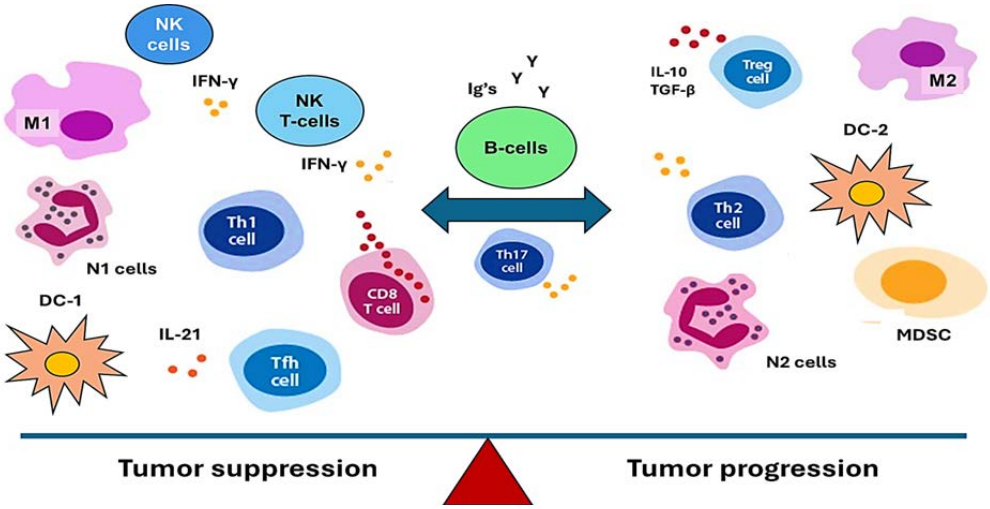

Figure 3. Dual Roles of Immune Cell Subsets in Tumour Immunity.

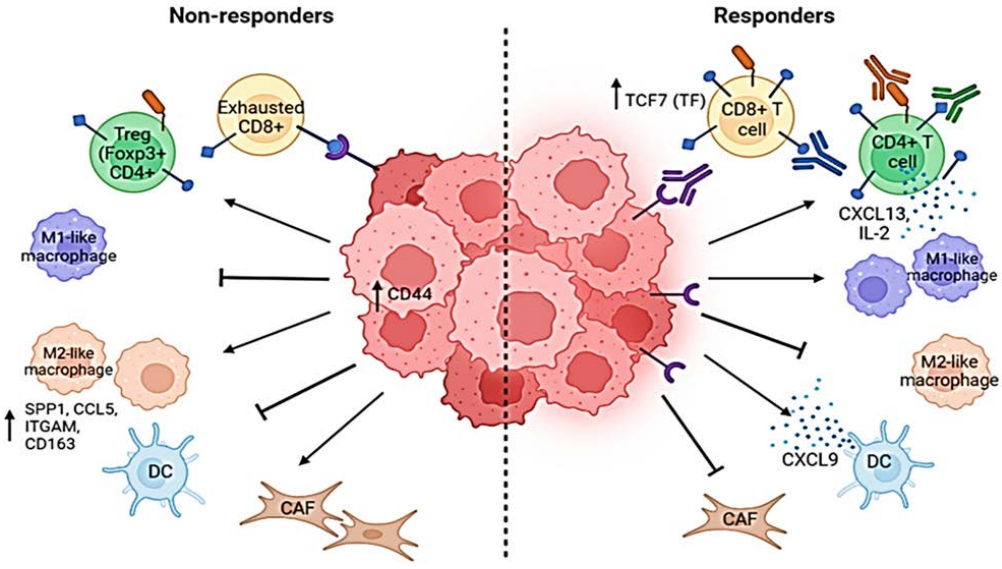

Figure 4. Cellular Landscape of Responders vs. Non-Responders in the Tumour Microenvironment.

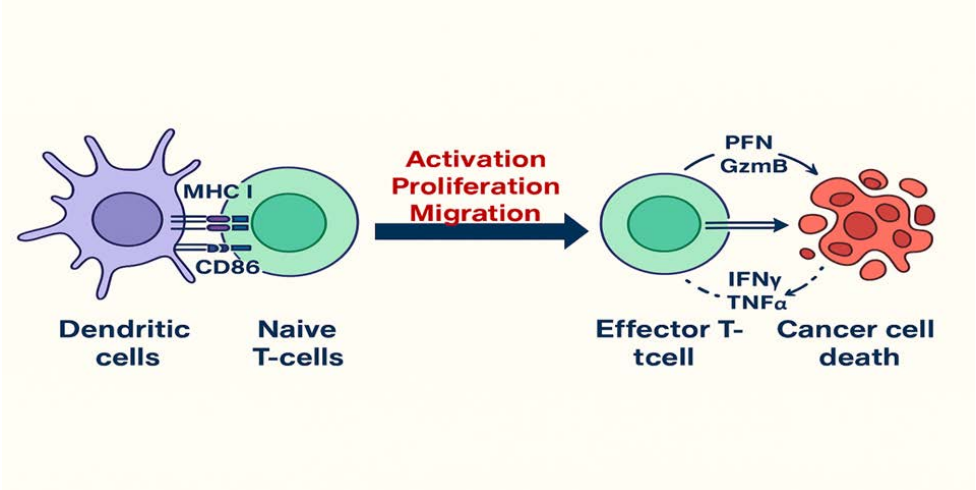

Figure 5. The stimulation of T cells (Adopted from BioRender[44])

Among TILs, cytotoxic cells serve as the first effectors of tumour cell apoptosis by releasing cytolytic molecules such as perforin and granzymes directly ($CD8^+$ cells). T cells also can fight cancers, which is why a greater density of T cells in the TME is associated with better prognosis[46].

Besides $CD4^+$ T cells which carry antitumor effects, TH1-type helper T cells provide the major constituent of immune defence by secreting distinct pro-inflammatory cytokines, such as IFN-γ, thereby assisting $CD8^+$ cytolysis and the activation of other effector arms of the immune system. Tregs achieve regulation of other T response activities and promote immune tolerance whilst inhibiting effective antitumor immunity. Within the tumour microenvironment, Tregs exert suppressive activity against cytotoxic T cells through direct contact and secretion of suppressor cytokines such as TGF-β and IL-10[47].

ACT is one of the most potent immunotherapy strategies in which autologous T lymphocytes are separated from blood, expanded ex-vivo, and then infused back into the patient with the aim of strengthening antitumor immunity. Among the early and well-established approaches, one has involved TILs stimulated with IL-2, which has exhibited clinical efficacy, especially in advanced melanoma[22].

Carrying the nearest to completion a major step in advance of ACT has been for the T cells to be carcinoma antigen-dependent; these T cells get genetically modified to express synthetic receptors that detect tumour-specific antigens. T cells are first collected from the patient by means of apheresis, and then genetically modified to express CARs: these are extracellular components of hybrid or fusion proteins consisting of a single-chain variable fragment (scFv) that recognizes a tumour antigen and intracellular signalling domains such as CD3ζ and costimulatory molecules like CD28 or 4-1BB that provide a sustained activation signal to the T cells[48]. After modification, CAR T cells are expanded and reinfused into the patient to kill tumour cells in a targeted manner (Figure 6).

CAR T-cell treatment has shown remarkable clinical success, particularly in hematologic malignancies. FDA-approved CAR T cells directed against CD19 or BCMA have achieved exceedingly high remissions in acute lymphoblastic leukaemia (ALL), non-Hodgkin lymphomas, and multiple myeloma[49]. The first-generation CAR T cells manifested very little in vivo persistence, and second-generation CARs, which gain costimulatory domains from CD28 (Maher et al., 2002) or 4-1BB[50], on the contrary, improved survival and function.

Alongside CAR T-cell development, TCR, engineered T-cell therapy (TCR-T) has been created as another powerful ACT modality. The T cells are genetically modified in this therapy to express TCRs with recognition for tumour antigens in the context of MHC molecules. In early experiments, TCR gene transfer has demonstrated the potential to induce antitumor specificity in peripheral blood lymphocytes[51] and has achieved clinical benefit in melanoma patients. TCR-T therapies directed against cancer-testis antigens such as NY-ESO-1 have been able to produce durable clinical responses in several tumour types[52].

Indeed, both CAR T and TCR T-cell therapies have transformed the landscape of cancer immunotherapy; they provide highly personalized, antigen-specific approaches. Current research is thereby focusing on increasing efficacy in solid tumours, ensuring better persistence, and bringing down the incidence of adverse effects.

B Cells and Tumour Immunity

B cells are central to humoral immunity as they turn into antibody-secreting plasma cells. Apart from producing antibodies, B cells shape $CD4^+$ T cell responses and can act as professional APCs to activate T cells into responding to tumour-associated antigens, while by secreting cytokines, they influence the adaptive response[53].

Monoclonal antibodies have, nowadays, been the cornerstone of immunotherapeutic approaches, while therapies that centre on B cells stand as a promising alternative for cancer treatment[54]. Bregs or regulatory B cells, a rare and highly immunosuppressive subset that enable tumour immune evasion through processes such as interactions with immune cells and release of inhibitory cytokines like IL-10 and TGF-β[55]. B cells have also been implicated in the progression of a variety of cancers, including melanoma and breast and lung cancers-if we consider such a role-in contrast to their anti-tumorigenic role that varies depending on their activation state and interaction with various other cells in the TME[56].

According to the current beliefs, infiltrating B cells may inhibit cytotoxic T cell responses in the tumour microenvironment or may be immunosuppressive by the production of anti-inflammatory cytokines. On the contrary, the presence of $CD20^+$ B cells have been associated with good clinical outcomes in other cancers such as ovarian and non-small cell lung cancers. The B lymphocytes might be exerting their antitumor effects against the formation of tumour-specific antibodies and stimulation of T cell-mediated immunity (Figure 7).

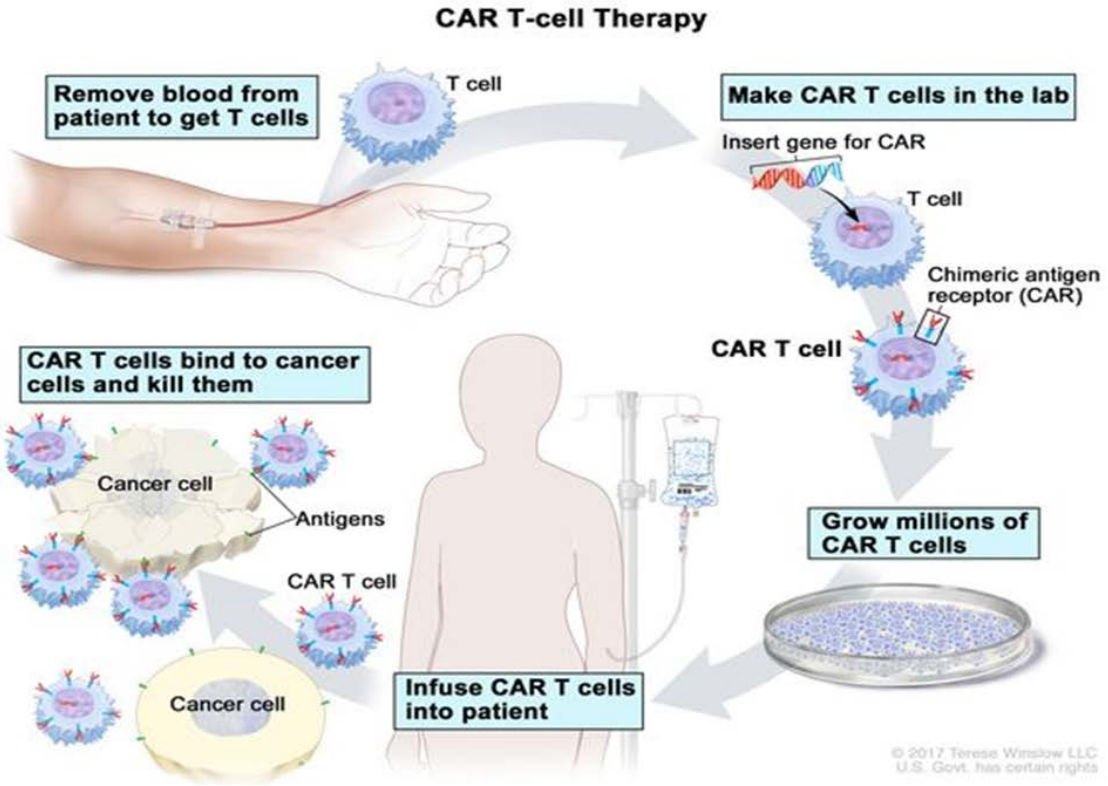

Figure 6. CAR T Cell Therapy

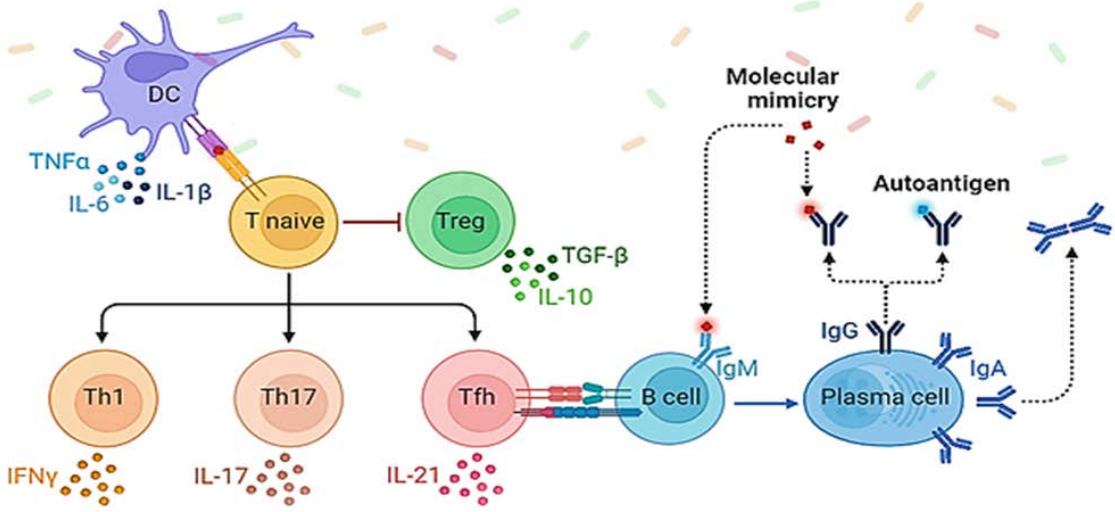

Figure 7. The Role of B cells in immunity.

Tertiary lymphoid structures (TLSs) are ectopic lymphoid aggregates in escape of secondary lymphoid organs of orderly array of B and T cells located in or near tumours. Their presence is often linked to better patient prognosis and a better response to treatment with immune checkpoint inhibitors and other immunotherapies across several tumour types[57]. Activated B cells hosted on TLSs can assist tumour response by antigen presentation to T cells and production of antibodies directed against tumour-associated antigens. In addition, cytokines secreted by B cells, including IFN-γ and IL-6, form a pro-inflammatory TME that endorses immune activation and tumour clearance[58].

Natural killer (NK) cells and cancer therapies

Natural killer (NK) cells serve mechanical functions in the innate immune system to recognize and eliminate malignant cells without having the previous sensitization. They perform cytotoxicity largely by displaying perforin and granzymes to facilitate the apoptotic death of target cells and also secrete pro-inflammatory cytokines such as IFN-γ and TNF-α, which help promote antitumor immune responses[59]. The undesired, suppressive conditions set by the TME, resulting from such factors as prostaglandin E2 and elevations in inhibitory receptors such as KIRs, can really interfere with NK cell functions[60].

Owing to recent advances in NK cell-based immunotherapies, adoptive NK cell transfer presents itself an attractive, less toxic alternative to T-cell-based strategies. These methodologies include genetically modifying NK cells with CARs to detect tumour antigens in an MHC-independent manner. CAR-NK cells outperform CAR-T cells in certain ways, including having a diminished probability of CRS and GvHD, being safer in an allogeneic context, and harbouring natural antitumor ability[61].

Several mechanisms allow NK cells to enact cytotoxicity through direct lysis via perforin and granzymes, through cytokine production, and ADCC through CD16[62]. Genetic modification to generate CAR-NK cells normally involves retrovirus or lentiviral-based vectors. While retroviruses provide stable integration within the genome, they carry the chance of insertional mutagenesis that might also impair NK cell viability. Lentiviral vectors are safer, however, due to low transduction efficiency, one must repeat the process several times to achieve complete transduction[62]. For the non-viral ways of delivering, transient gene expression through electroporation or liposome-based transfection is chosen to reduce the risk of mutagenesis; unfortunately, it remains impeded by expression duration. In contrast, DNA transposon systems (Sleeping Beauty, PiggyBac) are trying to support the triplet of safety, integration capacity, and gene cargo size, and still require some assistance in increasing efficiency and cell viability[10].

The immunosuppressive nature of the TME renders CAR-NK therapies into several challenges when dealing with the solid tumour. Hypoxia, lack of nutrients, suppressive cytokines, and inhibitory receptor-ligand interactions are some of the causes for NK-cell dysfunction. To counter these challenges, literature put forward the strategies of the NK cells themselves expressing cytokines such as IL-2 or IL-15 to promote their survival[63], metabolic reprogramming interventions to circumvent TME-imposed metabolic limitations[64], and checkpoint blockade with an emphasis on PD-L1, LAG-3, and TIGIT molecules[65]. On top of these approaches, CAR-NK cells can also be engineered to express chemokine receptors to increase their trafficking capacity toward the tumour[66].

NK cell receptor signal modulation is expected to increase therapeutic efficacy. Several monoclonal antibodies against inhibitory receptors such as KIRs and NKG2A have shown promise, especially with Monalizumab (anti-NKG2A) undergoing clinical investigation[67]. On the other hand, strong emphasis and an increase in activating receptor expression through binding of the NKG2D receptor to the stress ligands, such as MICA/MICB, are being studied[67]. Therefore, CAR-NK therapy offers the most promising, adaptable, and safer alternative to cancer treatment, particularly for refractory or advanced solid tumours. Its safety profile and alternate means of cytotoxicity make it an attractive option against CAR-T therapies; however, in curing cases of patients, there is a need to handle the shortcomings inherent in current techniques and biologics, especially in the TME. There is ongoing research that focuses on CAR modification, prolonged NK cell persistence, and alteration of the tumour milieu to establish wider clinical implementation of CAR-NK strategies (Figure 8).

Myeloid cells and tumour immunity

Within the myeloid lineage, granulocytes and mononuclear phagocytes perform several tasks relating to immunity in cancer. Neutrophils have been the cells most associated with defence against microorganisms; yet, their behaviour with respect to tumours is contradictory[68]. They help in the metastasis of tumour cells by helping CTCs[69], whereas an alternative pathway helps neutrophils promote T cell polarization and therefore, assist antitumor immunity[70]. They can have opposing effects in the TME depending on their state of functional polarization into N1 antitumorigenic and N2 pro-tumorigenic phenotypes[71].

Mononuclear phagocyte cells comprising monocytes, macrophages, and dendritic cells (DCs) serve in the immune response, both innate and adaptive. Plasmacytoid DCs (pDCs) make most type I interferons and could induce immune activation or promote immune tolerance via Treg recruitment and immunosuppressive cytokine release[72]. The cDCs are further divided into cDC1s, which activate $CD8^+$ T cells through cross-presentation and produce CXCL9/10 to recruit effector cells[73]; and cDC2s, which mainly interact with $CD4^+$ T cells and are currently being investigated for their role in shaping TME immunity[74].

Tumour-associated macrophages exhibit an incredible degree of plasticity: in certain cases, they kill tumour cells through phagocytosis or antigen presentation; while in others, they may aid tumour progression by stimulating mechanisms such as angiogenesis, fibrosis, and immune suppression. Tumour-associated macrophages secrete VEGF during vascular remodelling[75]; they influence fibrosis through remodelling of the matrix[76]; and they affect T cell activity participating in both stimulatory (IL-12, CD86) and inhibitory (IL-10, PD-L1) pathways[77].

Dissecting Immune Heterogeneity with Single-Cell Technologies

Tumour-infiltrating lymphocytes (TILs) are sub-divided phenotypically-i.e., $CD8^+$ T cells, helper T cells (Th1, Th2, Th17), and Tregs-with each possessing different functional states of operation and spatial distribution within the TME[78]. Yet, traditional techniques cannot explain this heterogeneity.

Understanding TILs changed with the advent of single-cell screens. Mass cytometry (CyTOF) measures the presence of >40 proteins for each cell simultaneously using metal-conjugated antibodies[79], while scRNA-seq enables the gross profiling of transcriptomes, rare-population identification, and tracking cell lineages[80]. Targeting and mapping the tumour immune landscape are now pressing concerns that researchers can attempt to address using such techniques[81].

IDO1 as an Immune Modulator Therapy

Indoleamine 2,3-dioxygenase 1 is an intracellular cytoplasmic enzyme that contains a prosthetic heme group and it enable tumours to evade immune destruction[82]. IDO1 enzyme commences and controls the catabolism of tryptophan. It is the main enzyme of the kynurenine pathway catabolizing tryptophan. It is required to synthesise protein and niacin and serves also as a precursor for serotonin and melatonin. IDO1 is mostly found in mucosal tissues of the lung and placenta, where endothelial cells produce it; in the female genital tract, epithelial cells produce it; and in lymphoid tissues under normal conditions. When it is overexpressed, the kynurenine/tryptophan ratio goes up, which can be used to predict how cancer will grow and spread. The depletion of tryptophan and the production of kynurenine help many types of tumours suppress the immune system. Tryptophan depletion ultimately reduces T-cell proliferation, given that T-cells are particularly sensitive to tryptophan deficiency. Toxic downstream products of IDO1 can also cause macrophages and dendritic cells to become immunosuppressive[83]. Many studies have demonstrated the presence of IDO in breast cancer, colorectal cancer, and prostate cancer. Cancer cells can express IDO7, either autonomously or in response to inflammatory cytokines, such as IFN-γ13, secreted by tumour-infiltrating immune cells. Several immunological factors are believed to influence IDO1 expression. One of the most important factors influencing IDO function in various human cells is IFN-γ.

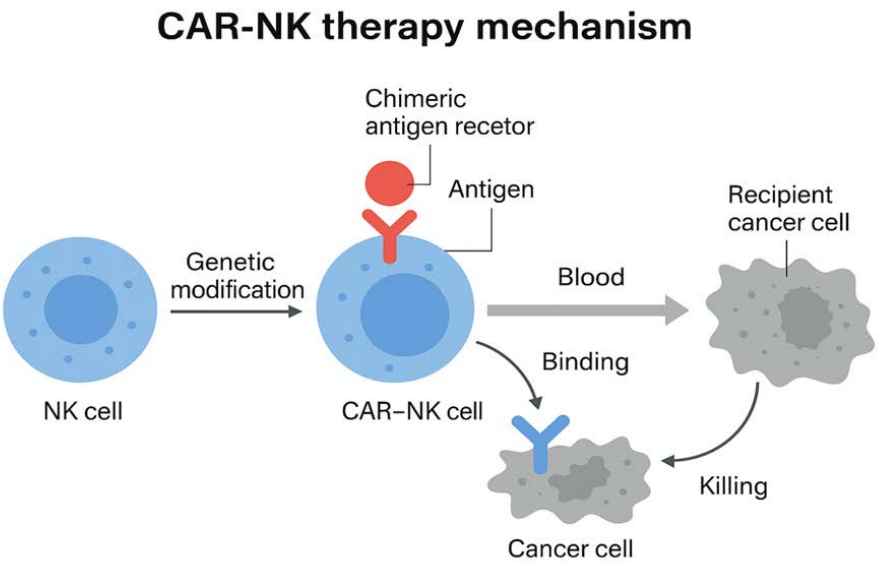

Figure 8. CAR-NK Therapy

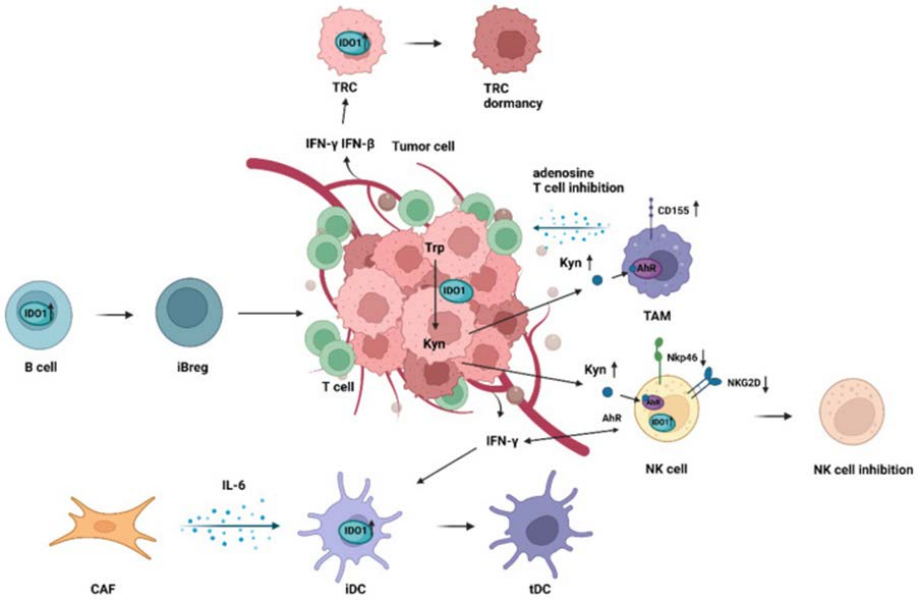

Figure 9. IDO mechanism[90].

IDO1 is an important immune checkpoint modulator that helps tumours escape the immune system. It is also a crucial target for treating cancer. Blocking IDO is a great way to bring back or improve the body's ability to fight cancer. IDO1 inhibitors have been effective when used together with immunotherapy, radiotherapy, or chemotherapy, even in cancers that usually don't respond well to these treatments[84]. Natural chemicals are important places to find drugs. Before 2010, when scientists started looking for IDO1 inhibitors, natural chemicals gave them important structural information that helped them make IDO1 inhibitors in a logical way[85].

In the tumour microenvironment, TILs are the major source of IFN-γ release[86]. Upon IFN-γ receptor activation, Jak kinases are phosphorylated. Phosphorylated JAK acts further to phosphorylate the signal transducer and activator of transcription protein 1 (STAT1)[87]. The IDO1 promoter contains several IFN-γ-responsive regions, including the interferon-stimulated response element (ISRE) and the IFN-γ activation sequence (GAS). IFN-γ activates the IDO1 through the JAK/STAT1 signalling pathway by activating the ISRE and GAS sequence elements[88]. IFN-γ also induces the production of IFN-γ-regulated factor 1 (IRF1) through NF-kB and STAT-1-dependent pathways. IRF1 binds to the ISRE in the promoter of the IDO1 gene, contributing to the transcription of IDO1 (Figure 9)[89].

Oncolytic Viruses and Tumour Immunity

Oncolytic virotherapy is one of the exciting enzymes in cancer immunotherapy, wherein genetically engineered viruses target tumour cells selectively with their dissolution, while generating secondary antitumor immune responses. These oncolytic viruses (OVs) replicate in malignant cells to induce immunogenic cell death or ICD and systemic immunity against them without injuring normal tissues[91,92].

As OVs thrombolize and lyse tumour cells in the process of the replication of tumour cells, the release of tumour-associated antigens

(TAAs) together with disorder signals, i.e., damage-associated molecular patterns (DAMPs), such as ATP, calreticulin (CRT), and HMGB1, constitutes seriously stimulating signals to activate dendritic cells and to initiate adaptive immune responses[92]. Meanwhile, not only local tumour invasion goes on, but also systemic immunity mediated by the $CD8^+$ cytotoxic T cells, $CD4^+$ helper T cells, and NK cells is stimulated so that immunological memory is enhanced and metastasis is prevented.

Perhaps most predominantly, these OVs were created to multiply selectively within tumour cells by exploiting cancer-specific mutations or signalling pathways. As infection proceeds, newest viral progeny spreads within the tumour microenvironment, increasing oncolysis and recruiting immune effectors to the site of the disease[93].

One of the most clinically advanced oncolytic viruses is Talimogene laherparepvec (T-VEC), a modified herpes simplex virus type 1 (HSV-1) engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF). T-VEC not only lyses tumour cells but, also promotes antigen presentation and T cell priming through the recruitment and activation of dendritic cells. Its efficacy in patients with unresectable metastatic melanoma has been validated in multiple clinical trials, leading to its FDA approval[94].

CONCLUSION

Cancer immunotherapy represents a paradigm shift in oncology, establishing a novel and potent treatment model. Over the past decade, immune checkpoint inhibitors (ICIs), adoptive T cell therapies encompassing CAR-T and CAR-NK, and oncolytic virus therapies have emerged as potent treatment options against several malignancies. Despite remarkable progress in immunotherapies, the immunosuppressive TME, interpatient variability in therapeutic responses, and treatment-associated toxicities remain major challenge and requiring further innovation. Nevertheless, the field is advancing rapidly driven by the single-cell technologies, high-dimensional profiling, and deeper insights into immune cell heterogeneity within the TME. Furthermore, combinations of immunotherapies with conventional treatments and immunotherapies with each other exhibit great potential for improving efficacy and overcoming resistance. Personalized immunotherapy guided by genomic and proteomic data and integrated with AI-powered diagnostics, has the potential to challenge and redefine the classic paradigm of cancer treatment. A great insight into immune regulation, tumour evolution, and cell therapy engineering needs to be harnessed to yield durable and safe responses across a large population of patients. Immunotherapy is a big step forward in the treatment of cancer because it gives patients with cancers that have been difficult to treat with the usual modalities hope for curing their disease. TMEs include different kinds of immune cells: T cells, B cells, NK cells, and myeloid cells. This is very important for tumour growth, immune evasion by the tumours, and the efficacy of immunotherapy. Emerging cancer therapies such as immunomodulators, oncolytic viruses, ACT, and ICIs harness the immune system to combat malignancies. Unlike conventional modalities such as surgery, chemotherapy and radiotherapy which are often limited by systemic toxicity, resistance, and poor efficacy in advanced disease This therapeutic evolution has transformed traditional therapeutic models in oncology to precision immunomodulation aimed at restoring effective antitumor immunity.

Authorship Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None

Competing Interest: None

Acceptance Date: 22 August 2025

REFERENCE

1. Liu B, Zhou H, Tan L, et al. Exploring treatment options in cancer: tumor treatment strategies. Signal Transduct Target Ther. 2024;9(1):175-86.
2. Marcus A, Gowen BG, Thompson TW, et al. Recognition of tumors by the innate immune system and natural killer cells. Adv Immunol 2014;122(1): 91-128.
3. Zhang M, Liu C, Tu J, et al. Advances in cancer immunotherapy: historical perspectives, current developments, and future directions. Mol Cancer 2025;24(1):136-48.
4. Xu L, Ye L, Huang Q. Tissue-Resident Memory CD8+ T Cells: Differentiation, Phenotypic Heterogeneity, Biological Function, Disease, and Therapy. MedComm 2025;6(3):1-17
5. Ostrand-Rosenberg S. Looking to the future of cancer immunotherapy: many questions to answer and many therapeutic opportunities. Cancer Immunol Immunother 2013;62(1):1-2.
6. Bilotta MT, Antignani A, Fitzgerald DJ. Managing the TME to improve the efficacy of cancer therapy. Front Immunol 2022;13(9):1-19
7. Feng Y, Tang Q, Wang B, et al. Targeting the tumor microenvironment with biomaterials for enhanced immunotherapeutic efficacy. J Nanobiotechnology 2024;22(1):737-46.
8. Kim SK, Cho SW. The Evasion Mechanisms of Cancer Immunity and Drug Intervention in the Tumor Microenvironment. Front Pharmacol 2022;13(8):1-16.
9. Wei SC, Duffy CR, Allison JP. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. Cancer Discov 2018;8(9):1069-86.
10. Baghy K, Ladányi A, Reszegi A, et al. Insights into the Tumor Microenvironment-Components, Functions and Therapeutics. Int J Mol Sci 2023;24(24): 1-12.
11. Yaping W, Zhe W, Zhuling C, et al. The soldiers needed to be awakened: Tumor-infiltrating immune cells. Front Genet 2022;13(9):1-18.
12. Accogli T, Bruchard M, Végran F. Modulation of CD4 T Cell Response According to Tumor Cytokine Microenvironment. Cancers (Basel) 2021;13(3):1-13.
13. Wang H, Zhou F, Qin W, et al. Metabolic regulation of myeloid-derived suppressor cells in tumor immune microenvironment: targets and therapeutic strategies. Theranostics 2025;15(6):2159-84.
14. Raskov H, Orhan A, Christensen JP, et al. Cytotoxic CD8(+) T cells in cancer and cancer immunotherapy. Br J Cancer 2021;124(2):359-67.
15. Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. Cell Mol Life Sci 2020;77(9):1745-70.
16. Wu X, Yang X, Dai Y, et al. Single-cell sequencing to multi-omics: technologies and applications. Biomark Res 2024;12(1):110-7.
17. Ramesh RPG, Yasmin H, Ponnachan P, et al. Phenotypic heterogeneity and tumor immune microenvironment directed therapeutic strategies in pancreatic ductal adenocarcinoma. Front Immunol 2025;16(1):1-15.

18. Deng W, Ma Y, Su Z, et al. Single-cell RNA-sequencing analyses identify heterogeneity of CD8(+) T cell subpopulations and novel therapy targets in melanoma. Mol Ther Oncolytics 2021;20(105):1-18.
19. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol 2020;17(8):807-21.
20. Palma M. Advancing Breast Cancer Treatment: The Role of Immunotherapy and Cancer Vaccines in Overcoming Therapeutic Challenges. Vaccines (Basel) 2025;13(4):1-11.
21. Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor microenvironment. Nat Immunol 2013;14(10):1014-22.
22. Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. Nat Rev Immunol 2012;12(4):269-81.
23. Rosenberg SA, Parkhurst MR, Robbins PF. Adoptive cell transfer immunotherapy for patients with solid epithelial cancers. Cancer Cell 2023;41(4):646-8.
24. Tang L, Pan S, Wei X, et al. Arming CAR-T cells with cytokines and more: Innovations in the fourth-generation CAR-T development. Mol Ther 2023;31(11):3146-62.
25. Shiravand Y, Khodadadi F, Kashani SMA, et al. Immune Checkpoint Inhibitors in Cancer Therapy. Curr Oncol 2022;29(5):3044-60.
26. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. Nat Rev Immunol 2013;13(4):227-42.
27. Callahan MK, Wolchok JD, Allison JP. Anti-CTLA-4 antibody therapy: immune monitoring during clinical development of a novel immunotherapy. Semin Oncol 2010;37(5):473-84.
28. Graziani G, Lisi L, Tentori L, et al. Monoclonal Antibodies to CTLA-4 with Focus on Ipilimumab. Exp Suppl 2022;113(1):295-350.
29. Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26(1):677-704.
30. Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res 2020;10(3):727-42.
31. Qiu Y, Ke S, Chen J, et al. FOXP3+ regulatory T cells and the immune escape in solid tumours. Front Immunol 2022;13(9):1-18.
32. Li X, Shao C, Shi Y, Han W. Lessons learned from the blockade of immune checkpoints in cancer immunotherapy. J Hematol Oncol 2018;11(1):1-13.
33. Arneth B. Molecular Mechanisms of Immune Regulation: A Review. Cells 2025;14(4):1-11.
34. Casagrande S, Sopetto GB, Bertalot G, et al. Immune-Related Adverse Events Due to Cancer Immunotherapy: Immune Mechanisms and Clinical Manifestations. Cancers (Basel) 2024;16(7):1-13.
35. Weber JS, Hodi FS, Wolchok JD, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. J Clin Oncol 2017;35(7):785-92.
36. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36(17):1714-68.
37. Apalla Z, Rapoport B, Sibaud V. Dermatologic immune-related adverse events: The toxicity spectrum and recommendations for management. Int J Womens Dermatol 2021;7(5):625-35.
38. Das S, Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. J Immunother Cancer 2019;7(1):306-12.
39. Moeckel C, Bakhl K, Georgakopoulos-Soares I, et al. The Efficacy of Tumor Mutation Burden as a Biomarker of Response to Immune Checkpoint Inhibitors. Int J Mol Sci 2023;24(7):1-17.
40. Shen M, Du Y, Ye Y. Tumor-associated macrophages, dendritic cells, and neutrophils: biological roles, crosstalk, and therapeutic relevance. Med Rev (2021) 2021;1(2):222-43.
41. Zamarron BF, Chen W. Dual roles of immune cells and their factors in cancer development and progression. Int J Biol Sci 2011;7(5):651-8.
42. Liu Z, Zhou Z, Dang Q, et al. Immunosuppression in tumor immune microenvironment and its optimization from CAR-T cell therapy. Theranostics 2022;12(14):6273-90.
43. Bour-Jordan H, Bluestone JA. Regulating the regulators: costimulatory signals control the homeostasis and function of regulatory T cells. Immunol Rev 2009;229(1):41-66.
44. BioRender. T Cell Activation and Differentiation (Layout) [internet]. 2025 [accessed on August 06, 20250.
45. Reinherz EL. αβ TCR-mediated recognition: relevance to tumor-antigen discovery and cancer immunotherapy. Cancer Immunol Res 2015;3(4):305-12.
46. Disis ML, Bernhard H, Jaffee EM. Use of tumour-responsive T cells as cancer treatment. Lancet 2009;373(9664):673-83.
47. Chaudhary B, Elkord E. Regulatory T Cells in the Tumor Microenvironment and Cancer Progression: Role and Therapeutic Targeting. Vaccines (Basel) 2016;4(3):1-11.
48. Andrea AE, Chiron A, Sarrabayrouse G, et al. A structural, genetic and clinical comparison of CAR-T cells and CAR-NK cells: companions or competitors? Front Immunol 2024;15(1):1-11.
49. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. Nat Rev Clin Oncol 2023;20(6):359-71.
50. Whilding LM, Maher J. CAR T-cell immunotherapy: The path from the by-road to the freeway? Mol Oncol 2015;9(10):1994-2018.
51. Shafer P, Kelly LM, Hoyos V. Cancer Therapy With TCR-Engineered T Cells: Current Strategies, Challenges, and Prospects. Front Immunol 2022;13(8):1-13.
52. Thomas R, Al-Khadairi G, Roelands J, et al. NY-ESO-1 Based Immunotherapy of Cancer: Current Perspectives. Front Immunol 2018;9(947):1-11.
53. Rastogi I, Jeon D, Moseman JE, et al. Role of B cells as antigen presenting cells. Front Immunol 2022;13(9):1-15.
54. Zahavi D, Weiner L. Monoclonal Antibodies in Cancer Therapy. Antibodies (Basel) 2020;9(3):1-17.
55. Catalán D, Mansilla MA, Ferrier A, et al. Immunosuppressive Mechanisms of Regulatory B Cells. Front Immunol 2021;12(6):1-11.
56. Gupta SL, Khan N, Basu S, et al. B-Cell-Based Immunotherapy: A Promising New Alternative. Vaccines (Basel) 2022;10(6):1-12.
57. Zhang Q, Wu S. Tertiary lymphoid structures are critical for cancer prognosis and therapeutic response. Front Immunol 2022;13(1):1-16.
58. Laumont CM, Banville AC, Gilardi M, et al. Tumour-infiltrating B cells: immunological mechanisms, clinical impact and therapeutic opportunities. Nat Rev Cancer 2022;22(7):414-30.
59. Paul S, Lal G. The Molecular Mechanism of Natural Killer Cells Function and Its Importance in Cancer Immunotherapy. Front Immunol 2017;8(1):1-12.
60. Morcillo-Martín-Romo P, Valverde-Pozo J, Ortiz-Bueno M, et al. The Role of NK Cells in Cancer Immunotherapy: Mechanisms, Evasion Strategies, and Therapeutic Advances. Biomedicines 2025;13(4):1-10.

61. Ahmad GV, Nouri S, Mohammad gholian A, et al. Breaking barriers: CAR-NK cell therapy breakthroughs in female-related cancers. Biomedicine & Pharmacotherapy 2025;187(1):1-17.
62. Ham H, Medlyn M, Billadeau DD. Locked and Loaded: Mechanisms Regulating Natural Killer Cell Lytic Granule Biogenesis and Release. Front Immunol 2022;13(8):1-17.
63. Balkhi S, Zuccolotto G, Di Spirito A, et al. CAR-NK cell therapy: promise and challenges in solid tumors. Front Immunol 2025;16(1):1-15.
64. Lim SA. Metabolic reprogramming of the tumor microenvironment to enhance immunotherapy. BMB Rep 2024;57(9):388-99.
65. Tobin JWD, Bednarska K, Campbell A, et al. PD-1 and LAG-3 Checkpoint Blockade: Potential Avenues for Therapy in B-Cell Lymphoma. Cells 2021;10(5):1-12.
66. Li W, Wang X, Zhang X, et al. CAR-NK Cell Therapy: A Transformative Approach to Overcoming Oncological Challenges. Biomolecules 2024;14(8):1-13.
67. Zhang C, Hu Y, Shi C. Targeting Natural Killer Cells for Tumor Immunotherapy. Front Immunol 2020;11(60):1-11.
68. Yao J, Ji L, Wang G, et al. Effect of neutrophils on tumor immunity and immunotherapy resistance with underlying mechanisms. Cancer Commun (Lond) 2025;45(1):15-42.
69. Chen Q, Zou J, He Y, et al. A narrative review of circulating tumor cells clusters: A key morphology of cancer cells in circulation promote hematogenous metastasis. Front Oncol 2022;12(9):1-14.
70. Wang Z, Hu H, Bao Y, et al. Neutrophils in cancer: from immune defense to tumor promotion. Cancer Biol Med 2025;22(6):598-617.
71. Obeagu EI, Ezeala CC. Neutrophils as key regulators of tumor microenvironment in breast cancer: a focus on N1 and N2 polarization. Ann Med Surg (Lond) 2025;87(6):3509-22.
72. Ngo C, Garrec C, Tomasello E, et al. The role of plasmacytoid dendritic cells (pDCs) in immunity during viral infections and beyond. Cellu Molecular Immun 2024;21(9):1008-35.
73. Piot C, Pereira da Costa M, Biram A, et al. Spatial Organisation of Tumour cDC1 States Correlates with Effector and Stem-Like CD8(+) T Cells Location. Eur J Immunol 2025;55(8):1-17.
74. Tatsumi N, Kumamoto Y. Role of mouse dendritic cell subsets in priming naive CD4 T cells. Curr Opin Immunol 2023;83(1):1-12.
75. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. Immunity 2014;41(1):49-61.
76. Kulkarni T, O'Reilly P, Antony VB, et al. Matrix Remodeling in Pulmonary Fibrosis and Emphysema. Am J Respir Cell Mol Biol 2016;54(6):751-60.
77. Rivas JR, Liu Y, Alhakeem SS, et al. Interleukin-10 suppression enhances T-cell antitumor immunity and responses to checkpoint blockade in chronic lymphocytic leukemia. Leukemia 2021;35(11):3188-200.
78. Xie Q, Ding J, Chen Y. Role of CD8(+) T lymphocyte cells: Interplay with stromal cells in tumor microenvironment. Acta Pharm Sin B 2021;11(6):1365-78.
79. Bjornson ZB, Nolan GP, Fantl WJ. Single-cell mass cytometry for analysis of immune system functional states. Curr Opin Immunol 2013;25(4):484-94.
80. Nguyen A, Khoo WH, Moran I, et al. Single Cell RNA Sequencing of Rare Immune Cell Populations. Front Immunol 2018;9(1):1-15.
81. Antoranz A, Van Herck Y, Bolognesi MM, et al. Mapping the Immune Landscape in Metastatic Melanoma Reveals Localized Cell-Cell Interactions That Predict Immunotherapy Response. Cancer Res 2022;82(18):3275-90.
82. Song X, Si Q, Qi R, et al. Indoleamine 2,3-Dioxygenase 1: A Promising Therapeutic Target in Malignant Tumor. Front Immunol 2021;12(8):1-10.
83. Mbongue JC, Nicholas DA, Torrez TW, et al. The Role of Indoleamine 2, 3-Dioxygenase in Immune Suppression and Autoimmunity. Vaccines (Basel) 2015;3(3):703-29.
84. Le Naour J, Galluzzi L, Zitvogel L, et al. Trial watch: IDO inhibitors in cancer therapy. Oncoimmunology 2020;9(1):1-17.
85. Tan Y, Liu M, Li M, et al. Indoleamine 2, 3-dioxygenase 1 inhibitory compounds from natural sources. Front Pharmacol 2022;13(1):1-14.
86. Jorgovanovic D, Song M, Wang L, et al. Roles of IFN-γ in tumor progression and regression: a review. Biomark Res 2020;8(49):1-17.
87. Liu X, Ye L, Bai Y, et al. Activation of the JAK/STAT-1 signaling pathway by IFN-gamma can down-regulate functional expression of the MHC class I-related neonatal Fc receptor for IgG. J Immunol 2008;181(1):449-63.
88. Robinson CM, Shirey KA, Carlin JM. Synergistic transcriptional activation of indoleamine dioxygenase by IFN-gamma and tumor necrosis factor-alpha. J Interferon Cytokine Res 2003;23(8):413-21.
89. Meireson A, Devos M, Brochez L. IDO Expression in Cancer: Different Compartment, Different Functionality? Front Immunol 2020;11(5):1-13.
90. Huang X, Zhang F, Wang X, et al. The Role of Indoleamine 2, 3-Dioxygenase 1 in Regulating Tumor Microenvironment. Cancers (Basel) 2022;14(11):1-13.
91. Achard C, Surendran A, Wedge ME, et al. Lighting a Fire in the Tumor Microenvironment Using Oncolytic Immunotherapy. EBioMedicine 2018;31(1):17-24.
92. Volovat SR, Scripcariu DV, Vasilache IA, et al. Oncolytic Virotherapy: A New Paradigm in Cancer Immunotherapy. Int J Mol Sci 2024;25(2):1-13.
93. Ma R, Li Z, Chiocca EA, et al. The emerging field of oncolytic virus-based cancer immunotherapy. Trends Cancer 2023;9(2):122-39.
94. Bommareddy PK, Patel A, Hossain S, et al. Talimogene Laherparepvec (T-VEC) and Other Oncolytic Viruses for the Treatment of Melanoma. Am J Clin Dermatol 2017;18(1):1-15.