

REVIEW ARTICLE

Mechanisms of resistance to immunotherapy in lung cancer: A review

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Abstract

Pulmonary carcinomas have developed several mechanisms to evade immune cell attack. Among these mechanisms, the programmed death 1 (PD-1), programmed death ligand 1 and 2 (PD-L1/2), and the cytotoxic T-lymphocyte-associated protein 4 system have garnered particular interest. Tumor cells and lymphocytes express ligands for PD-1, which induce apoptosis or exhaustion of CD8 T cells. This further impacts the microenvironment (MEV) composed of cytokines, leading to immune tolerance. Therapies targeting PD-L1 expression have shown significant success in restoring the function of T-lymphocytes against tumor cells. Antibodies against the PD-1 receptor have been developed and tested in clinical trials with positive outcomes. Immunohistochemistry tests for PD-1 and PD-L1 expression are used to select patients likely to respond to this therapy. A strong PD-L1 staining in at least 1% of tumor cells and/or lymphocytes (or 50% in one trial) was considered a positive result and was associated with patient prognosis. This criterion was used to determine eligibility for anti-PD-L1 therapy. However, PD-L1 expression thresholds vary across clinical trials and therapeutic agents, with some drugs requiring PD-L1 positivity in $\geq 50\%$ of tumor cells. Based on data from previous clinical trials, most patients were diagnosed using this simple staining method. However, false-positive and false-negative results have been reported in some patients. Resistance and immune escape mechanisms of pulmonary carcinoma have been extensively investigated. Some of these mechanisms involve the metabolic reprogramming of tumor cells within the tumor MEV. Several immune checkpoint molecules have been identified and further tested. In addition, the composition of the tumor stroma, including various types of lymphocytes and dendritic cells, has gained considerable attention.

Keywords: Programmed death 1-programmed death ligand 1; Cytotoxic T-lymphocyte-associated protein 4; Lymphocyte activation gene 3; T-cell immunoglobulin and mucin domain-3; Glucocorticoid-induced tumor necrosis factor receptor family-related protein; Cytotoxic T cell; Dendritic cell; Metabolites

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1. Introduction

Immunotherapy was first introduced in melanoma and soon expanded to non-small cell lung cancer (NSCLC). Its development began with the detection of immune checkpoint molecules, particularly cytotoxic T-lymphocyte antigen 4 (CTLA4) and

programmed cell death 1 (PD-1). CTLA4 is expressed on dendritic cells (DCs) and regulatory T lymphocytes (Treg). Previous studies reported that the immune tolerance of tumor cells is mediated by the expression of PD-1 ligand (PD-L1), which induces the apoptosis of lymphocytes.^{1,2} Subsequently, antibodies targeting PD-1 and PD-L1 were developed and tested. These antibodies reversed the tolerance mechanisms of PD-1- and PD-L1-expressing tumor cells against T-lymphocytes, inducing tumor cell death.²⁻¹⁰ Currently, several pharmaceutical companies have developed checkpoint inhibitors (humanized monoclonal antibodies) for the treatment of NSCLC patients, and numerous Phase II and III studies have been conducted. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved three of these drugs for the treatment of NSCLC, and more have been added since then. Some of these drugs are selectively approved for squamous cell carcinomas, while others are indicated for all NSCLC subtypes.^{9,11-14} However, PD-1 and PD-L1 inhibitors are generally ineffective in treating SCLCs, as most do not express PD-1 or PD-L1. A few exceptions include *POU2F3*-expressing SCLC—associated with a non-neuroendocrine variant—and stroma cells. Nevertheless, clinical trials are currently investigating the use of immunotherapy in combination with chemotherapy.¹⁵⁻¹⁷

2. Checkpoint molecules

Tumor cells and lymphocytes may express PD-1 or PD-L1, which interact with corresponding receptors on cytotoxic CD8⁺ T cells, leading to immune tolerance or the apoptosis of the T cells.⁴ In addition, the PD-1/PD-L1 pathway influences the cellular microenvironment (MEV) by modulating cytokines, further promoting immune tolerance. Several solid malignancies have been successfully treated using antibodies against PD-L1, which activate cytotoxic T-lymphocytes and achieve cytotoxicity against tumor cells.^{3,6,10} Other than the common antibodies against PD-L1, antibodies against PD-1 have also been applied in clinical trials with favorable outcomes.^{2,4,5,7,8} Immunohistochemistry tests were implemented to select potential patients who might respond to PD-L1 treatment based on the expression of PD-1 and PD-L1. A strong staining in at least 1% of tumor cells and/or lymphocytes (or 50% in one trial¹⁸) was considered a positive result associated with patient prognosis, reflecting clinical thresholds whereby nivolumab may be administered with $\geq 1\%$ PD-L1-positive tumor cells, whereas pembrolizumab requires $\geq 50\%$ positivity for use as first-line therapy. Clinical data analysis indicates that immunohistochemistry tests were applied to identify patients (Figure 1). However, not all patients responded as expected: some

PD-1/PD-L1-positive patients did not respond to the test (false negative), while some PD-1/PD-L1-negative patients responded to the test (false positive).¹⁹⁻²¹ This resulted in the removal of one of the PD-L1 antibodies, nivolumab (FDA and EMA approved), from the immunohistochemical tests. However, many clinics in most European Union countries often request PD-L1 tests. In neoadjuvant therapy combined with chemotherapy, a positivity for $\geq 1\%$ of tumor cells is also required for nivolumab. For another drug (pembrolizumab), a test result with $\geq 50\%$ positive tumor cells is required to be eligible for monotherapy using the PD-L1-antibody. In second-line treatment, positivity has to be $\geq 1\%$, while for atezolizumab in first- and second-line treatments, tumor cell positivity should be $\geq 50\%$. Alternatively, an immune score of $\geq 10\%$ could also be used. For durvalumab, tumor cell scores should be $\geq 1\%$,²² and for cemiplimab, the tumor cell score should be $\geq 50\%$ for first-line monotherapy or $\geq 1\%$ if combined with chemotherapy. This resulted in a reflex basis for the PD-L1 tests conducted in Austria.

The expression of neoantigens is also crucial for the response of cytotoxic lymphocytes (Tcyt). If tumors do not express sufficient neoantigens, even a fully functional immune system may fail to eliminate tumor cells.²³ Furthermore, the immunogenicity of some neoantigens may be insufficient to trigger an effective immune response.²⁴⁻²⁶ This led to the evaluation of mutational burden (MTB), with the expectation that patients with a high MTB would respond better to immunotherapy.^{27,28} It was confirmed that a PD-L1 expression on tumor cells with a high MTB better identifies patients likely to benefit from immunotherapy.^{27,29,30} However, these combined tests do not encompass all patients. Therefore, beyond the presence of numerous neoantigens, the role of the major histocompatibility complex (MHC) on cytotoxic lymphocytes is also considered crucial. Despite these, a more selective presentation is still essential. For instance, aberrantly expressed or overexpressed non-mutated proteins from trophoblasts or cancer-testis proteins—such as the melanoma antigen cluster, previously used for vaccination—will bind to MHC-I molecules and elicit only a transient immune reaction.^{23,31,32} Mutated neoantigens can bind to MHC-II molecules and elicit a significant and lasting immune reaction. One example is the proteins derived from the mutated *TP53* gene in cigarette smokers. To recognize a tumor neoantigen as non-self and immunogenic, MTB was established as a method to analyze the number of mutations in a given tumor.^{30,33} Different types of next-generation sequencing platforms, such as whole-exome sequencing, whole-genome sequencing, or cancer gene panel sequencing, can be employed. Cutoffs have been used to distinguish between high- and

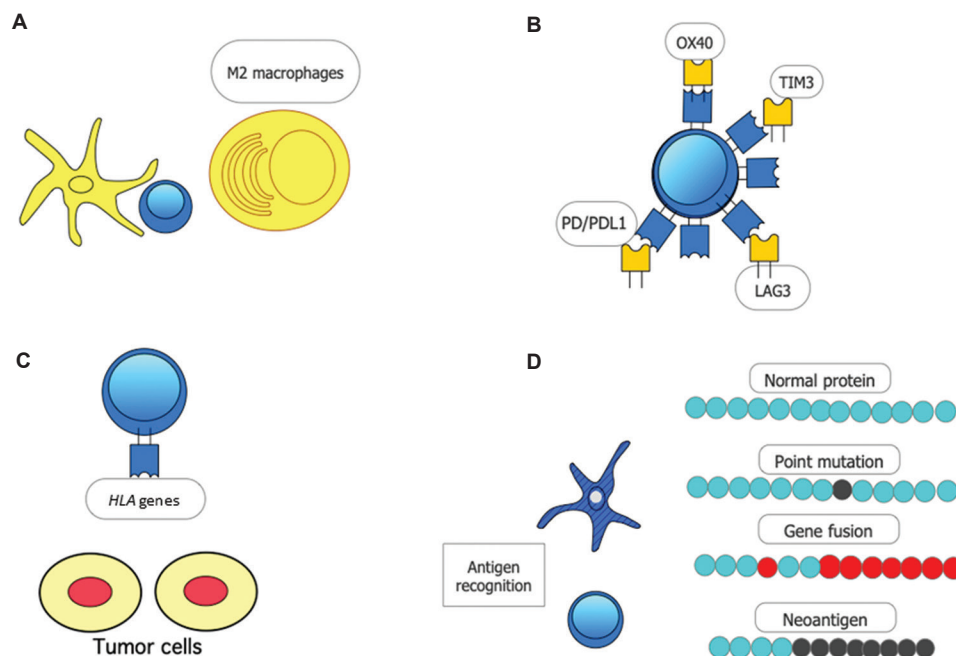


Figure 1. A scheme demonstrating various reactions of the immune system towards infiltrating tumor cells. (A) Cooperation between antigen-presenting cells and plasma cells results in polarization of macrophages into the M2 type. (B) Different activating (OX40) and deactivating (tolerogenic) molecules on T lymphocytes can cause tolerance or activation. (C) Different types of *HLA* genes and polymorphisms might either act in favor of tumor attack or silence. (D) The role of antigens presented by tumor cells. Normal proteins will cause self-tolerance, point mutations might result in low antigenicity, and gene fusion might either produce a non-self-antigen, depending on the type of exposed antigen, or a neoantigen, which will likely produce a strong antigenic signal. Image created by the author using ConceptDraw.

Abbreviations: LAG3: Lymphocyte activation gene 3; OX40: Tumor necrosis factor superfamily member 4; PD/PD-L1: Programmed death/Programmed death ligand 1; TIM3: T-cell immunoglobulin and mucin domain-3.

low-MTB. A novel investigation method was developed to analyze the T-cell receptor (TCR) on Tcvt by evaluating the recognition of tumor neoantigens. This method showed a good correlation with response to immunotherapy;^{23,29,34-36} however, the optimum TCR ($\alpha\beta$ or $\gamma\delta$) for the test remains uncertain.³⁷ Tumoricidal effects have been achieved by stimulating both types of T lymphocytes with neoantigens.

Another challenge in estimating the efficacy of PD-L1 therapy is the flexibility of the PD-L1 binding site. An immune reaction will be triggered if PD-L1 binds to PD-1. In contrast, a binding to B7.1 on DC induces an interaction with T cells and improves survival.³⁸ Runt-related transcription factor 3 (RUNX3) plays a crucial role in overcoming this challenge through the association with lymphocyte activation gene 3 (LAG3), CTLA4, PD-1, and T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains. *RUNX3* upregulates the chemokines *CCL3* and *CCL20*, increasing the infiltration of CD8⁺ T cells. Downregulation or inhibition of *RUNX3* suppresses infiltration of T cells.³⁹ An infiltration of CD8⁺ T cells within tumor cells generally predicts a good response in immunotherapy. Specifically, the expression of transcription factor 7 (TCF7) on these

T cells plays a crucial role. A high ratio of CD8⁺/TCF7⁺ to CD8⁺/TCF7⁻ T cells is a predictor of increased survival.²³

The binding of PD-L1 antibody may involve MHC class I, and polymorphisms in human leukocyte antigen (HLA) genes can influence the immune reaction against carcinoma cells (Figure 1C). For example, the *HLA-B44* allele is associated with prolonged survival in patients receiving immunotherapy,^{40,41} while certain germline mutations of *HLA* correlate with poorer responses.⁴²

During the search for other checkpoint molecules, several new inhibitors and accelerators have been identified. LAG3 and T-cell immunoglobulin and mucin domain-3 (TIM3) act as inhibitory molecules, whereas tumor necrosis factor superfamily member 4 (OX40) stimulates an immune reaction. Ongoing clinical studies are investigating combination therapies that target PD-L1 alongside LAG3 or TIM3. Similar to the PD-1/PD-L1 axis, LAG3 and TIM3 can induce immunotolerance. TIM3 is suspected to cause super-exhaustion of Tcvt. On the other hand, stimulation with OX40 analogs did not yield favorable outcomes. This may be due to the variable expression levels of PD-L1, OX40, and OX40 ligand among

NSCLCs, where low expression of OX40 was associated with an improved overall survival and a better prognosis. OX40, glucocorticoid-induced tumor necrosis factor receptor family-related protein (GITR), tumor necrosis factor superfamily member 9, and other receptors have been implicated in immune homeostasis. Although tumor regression was observed in experimental models, severe autoimmune reactions, likely linked to disruption of regulatory T cell (Treg) homeostasis, were reported.^{43–46}

Among these molecules, LAG3 is the most clinically advanced target. It is involved in the exhaustion of T cells, and combination treatment with anti-PD-L1 and anti-LAG3 has shown a significant clinical benefit compared to single-agent therapy. Coexpression of LAG3 and PD-L1 has been observed on both tumor cells and infiltrated lymphocytes, and dual blockade has demonstrated promising efficacy in countering PD-1 resistance.^{47,48} Therefore, the combination of anti-LAG3 and anti-PD-L1 treatment may soon receive the approval of the FDA and EMA. Recent studies on GITR inhibitors did not result in favorable outcomes. Clinical studies combining PD-L1 and TIM3 inhibitors are ongoing to explore their effect on PD-1 resistance, with TIM3 expression on lymphocytes regarded as a marker for super-exhaustion.^{49,50}

Previously, limited attention was given to the cells of the innate immune system and cells associated with lymphocytes. Before reviewing new protocols for restoring the immune response against cancer cells, it is essential to revisit the principles of immune responses, which will aid in understanding the detailed discussions that follow.

3. Immune cells and the tumor MEV

Tumor cells are either destroyed by cells of the innate or adaptive immune system or die due to hypoxia. Cellular debris must then be phagocytosed or removed by other mechanisms. Usually, macrophages and/or DCs process this debris and might select neoantigens from dying tumor cells to be presented to immune cells. In some cases, macrophages first present antigens to DCs, which further process them and ultimately present these antigens with costimulatory molecules to immune cells. Alternatively, antigens may be presented directly to natural killer (NK) cells or certain subtypes of T cells. The next step is the selection of MHC molecules. Presentation through MHC-II elicits a strong and potentially long-lasting immune reaction due to the generation of memory cells. In contrast, presentation through MHC-I generally triggers a milder and transient immune reaction. Another option for immune cells is to induce tolerance, which is crucial in avoiding immune reactions toward self-antigens. In these instances, antigen-bearing cells are eliminated through the cooperation of various immune system cells. The spatial

position of these cells is relevant. In the inflamed type of carcinoma, DCs and T lymphocytes are in proximity to the tumor cells, which enables direct cytotoxic action. However, in the other MEV types, this proximity is not present. Interventions are possible along this process.

A detailed analysis of the MEV of a given carcinoma is required to assess the effect of immunotherapy. Three types of MEV are discerned: the immune-inflamed, the immune-excluded, and the immune-desert tumor MEV (Figure 2).⁵¹ In the inflamed type, both CD4⁺ and CD8⁺ lymphocytes infiltrate the stroma and tumor cell nests. Carcinoma, as well as lymphocytes, express PD-L1/PD-1 along with regulatory molecules. This results in an effective and quick response for an anti-PD-L1 therapy. In the excluded type of MEV, lymphocytes are also present, but only in the surrounding stroma and not between the carcinoma cells. Activation of pathways such as the wntless-related integration site- β -catenin and transforming growth factor β (TGF β)^{52,53} results in immunotolerance and inhibition of the cytotoxic action of lymphocytes.^{54,55} In the desert type, lymphocytes are absent or scarce, and no response to immunotherapy is observed.^{23,51} Based on the current understanding, in this type of MEV, the endothelial cells inhibit the extravasation of immune cells. Research is still ongoing to better understand the underlying mechanisms and to identify options to interfere with this blockade.^{56–59} Some mechanisms, such as the *KEAP1* mutations in

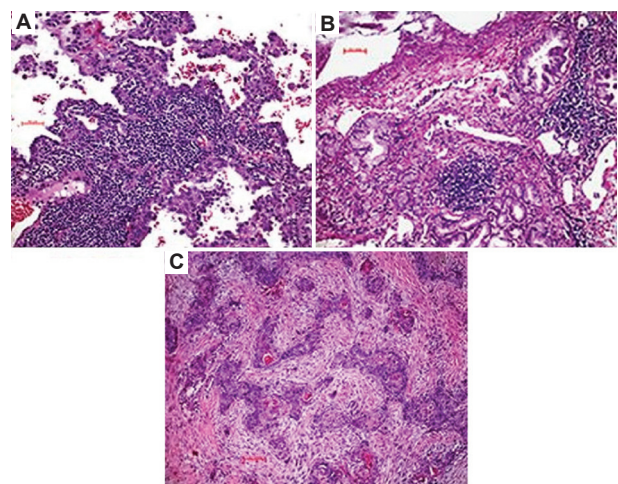


Figure 2. Three types of tumor microenvironment, stained with hematoxylin and eosin. (A) Papillary adenocarcinoma with microenvironment of the immune-inflamed type. Lymphocytes are infiltrating between the tumor cells. Scale bar: 50 μ m; (B) Acinar adenocarcinoma with microenvironment of the immune-excluded type. Lymphocytes are within the stroma, but do not infiltrate between the tumor nests/cells. Scale bar 100 μ m; (C) Keratinizing squamous cell carcinoma with microenvironment of the immune-desert type. There are no lymphocytes either within or in the vicinity of the carcinoma. However, there is an extensive proliferation of tumor-associated myofibroblasts. Scale bar 100 μ m. Source: Image by the author.

carcinoma that diminish the cooperation of DCs and T lymphocytes, have been identified. Recently, it was reported that adenocarcinomas with mutations in *KEAP1/STK11* genes are unresponsive to immunotherapy. However, if a combination of anti-PD-L1 and anti-CTLA4 is applied, this could be reversed to increase patients' survival.⁶⁰ Furthermore, inhibiting glutaminase can overcome those unresponsive carcinomas through the upregulation of the nuclear factor erythroid 2-related factor 2 pathway.⁶¹

Within the MEV, various immune cells are present, dominated by CD4 and CD8 lymphocytes, followed by B cells and neutrophils. The minority of cells is composed of macrophages, NK cells, and DCs. Within the DC population, plasmacytoid, classic DC (DC1c), and CD141-DC are observed.⁶² However, the MEV composition also influences prognosis. If CD4⁺ and CD8⁺ T cells, CD20/CD19⁺ B cells, M1 macrophages, and plasmacytoid DC are associated with tumor cells, this results in a favorable prognosis. If M2 macrophages dominate within the tumor, the prognosis is unfavorable (Figure 3A).⁶³ If Treg interacts with DC1c, these lymphocytes will inhibit the binding of DC to class II MHC, ultimately blocking immune reactions. In this condition, the action of NK cells is inhibited (Figure 3B). If the release of interferon (IFN)- γ

can be stimulated, this would block the polarization of DC1c toward Treg. However, several challenges remain. Differentiation of T cells into CD4⁺ T helper (TH) 1 cells causes a poor response to immune checkpoint inhibition;⁶⁴ in contrast, the cooperation of CD8⁺ and CD4⁺ T cells with DC1c cells induces a good response and prolongs patients' survival.⁶⁵

Recent research has focused on the action of DCs and their cooperation with macrophages and lymphocytes, particularly on the migration of DCs to the carcinoma (Figure 3C). When migrating to lymph nodes, DCs will reorganize their actomyosin cytoskeleton and reshape their cytoplasm. For nuclear envelope tension and translocation of cytosolic phospholipase A2 (cPLA2) into the nucleus, an upregulation of ARP2/3 is required. Once cPLA2 is within the nucleus, it activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and the expression of chemokine receptor type 7 (CCR7), which then causes migration into lymph nodes.⁶⁶ Another important enzyme involved in the immune reactions against carcinoma cells is the cyclic GMP-AMP synthase (cGAS). cGAS senses the presence of nucleic acids in DCs. Nucleic acids in the MEV are caused by carcinoma cell death and liberation of DNA and RNA fragments (nuclear debris). cGAS activates the stimulator of interferon genes (STING), which results in the release of proinflammatory cytokines and chemokines that promote a tumor-specific CD8⁺ T-cell response.⁶⁷ STING also activates DC1c, and this correlates positively with patient survival.⁶⁵ In the early stages of carcinoma development, an inflamed MEV with increased levels of IFN- γ causes an upregulation of interleukin (IL)-12 and suppresses IL-4. A blockade of IL-4 production enhances IL-12 synthesis and release by DC1c, and this expands the pool of tumor-infiltrating T cells. These DCs express maturation genes *CD40*, *CCR7*, and *IL12*, and immunoregulatory genes *CD274*, *PD-L2*, and *CD200*. In this scenario, the receptor tyrosine kinase AXL plays a key role.⁶⁸ On the contrary, if NF- κ B and signal transducer and activator of transcription (STAT) 3 are suppressed, DCs dysfunction; if this is reversed, the response to immunotherapy is restored.⁶⁹ Galectin-1, which is produced by lung cancer cells, can alter the phenotypes of DCs. It upregulates the inhibitor of DNA binding 3 (ID3) and IL-10 in CD11c-positive DC and also increases Treg (CD4⁺, CD25⁺, and forkhead box protein P3⁺), which altogether impairs the response to immunotherapy.⁷⁰ Another way to suppress the immune system is through the activation of signal co-integrator 3 (ASCC3). ASCC3 stabilizes STAT3 and recruits Cullin-associated and neddylation dissociated protein 1, which both impair the response of IFN-I.⁷¹ This decreases the number of CD8 T cells, NK cells, and DC cells, and increases Treg.

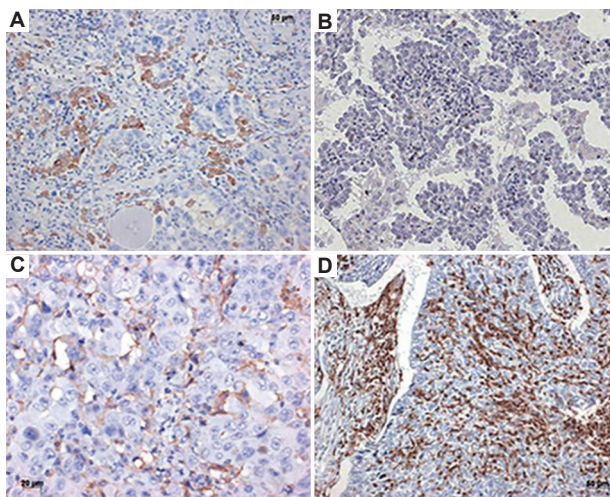


Figure 3. Immunohistochemistry test of tumor microenvironments. (A) M2 macrophages, which express CD206 and CD68. In most cases, the M2 cells are observed within the tumor, whereas M1 cells, which are cytotoxic for tumor cells, are outside the tumor area. Scale bar: 50 μ m; (B) NK cells (FOXP3⁺). In this case, scattered NK cells are present. In many other cases, only single cells are observed, indicating the inhibition of infiltration through various mechanisms. Scale bar: 20 μ m; (C) Monocytoid dendritic cells (CD64⁺ S100⁺). The proximate association of these antigen-presenting cells with the carcinoma cells is notable. Scale bar: 20 μ m; (D) MDSCs (CD11b⁺ CD15⁺). There are numerous MDSCs within this squamous cell carcinoma, and the cells are in proximity to the tumor cells. Scale bar: 50 μ m; Source: Image by the author. Abbreviations: NK: Natural killer; MDSC: Myeloid-derived suppressor cells.

Other approaches may be explored in the future, including inducing tumor antigen tolerance and lymphocyte exhaustion. Tolerance toward tumor antigens may not always depend on the PD-1-PD-L1 system, but on other regulatory pathways. This could explain the ineffectiveness of immunotherapy in some patients, despite having PD-L1-expressing carcinoma cells.

A very recent report described innate-like lymphocytes and NK-like cells. Within the lung parenchyma, resident lymphoid cells have been found. These cells can be subdivided into innate-like T cells, NK-like cells, and mucosa-associated invariant T cells. On their surface, various molecules are expressed, such as T-bet, GATA binding protein 3, and retinoic acid-related orphan receptor γ t.³⁷ Some cells are tumoricidal (type I cells), whereas others promote tumor growth (type II). Type I cells usually release granzyme, express tumor necrosis factor-related apoptosis-inducing ligand and IFN- γ , and induce apoptosis. On the contrary, innate-type II cells release IL-4, IL-10, IL-17, and TGF β , which promote tumor cell growth and angiogenesis.³⁷

3.1. Role of other cells in inducing immune tolerance

Within DCs, several subpopulations exist, including conventional DCs. These cells process tumor neoantigens and present them to CD8⁺ T lymphocytes as well as innate-like T lymphocyte type I, which in turn result in immune attacks. Other DCs, such as plasmacytoid and granulocytic DCs, induce immune tolerance by cooperating with Treg cells or inducing an MEV that promotes tumor cell invasion, spreading, and eventually metastasis.^{72,73}

Interaction of plasmacytoid DCs (Figure 3C) with monocytoic cells promotes the differentiation of macrophages into the tumor-friendly M2 type. In carcinogenesis, M2 macrophages induce angiogenesis, prepare and modulate matrix proteins that promote tumor cell growth, invasion, and metastasis (Figure 3A).^{74,75} On the other hand, M1 macrophages inhibit tumor progression in the early carcinogenesis as well as during metastasis formation.^{76,77} Carcinoma cells alone can influence the differentiation of M0-macrophages into M1 or M2 lineages. Activation of Notch signaling increases the formation of M1 macrophages, while blockade of Notch induces M2 formation. Recombinant signal binding protein for immunoglobulin κ J region-mediated Notch signaling regulates the M1 versus M2 polarization through suppressor of cytokine signaling 3 (SOCS3).⁷⁶ As Notch is mutated in several lung carcinomas, this may also influence differentiation signaling. However, studies are limited on this aspect. Furthermore, carcinoma cells can induce SOCS3 signaling and polarize macrophages into M2.

The accumulation of Treg at the tumor site can inhibit the anti-tumor effect and the influx of CD8⁺ T lymphocytes and NK cells into the tumor (Figure 3B).^{78,79} Myeloid-derived suppressor cells (MDSC) have been observed in pulmonary and squamous cell adenocarcinomas (Figure 3D). These cells not only inhibit cytotoxic T cells but also facilitate the proliferation of tumor cells by stimulating metabolism under hypoxia.⁸⁰⁻⁸³ A recent study reported that the metabolic condition can influence the infiltration of MDSC. In breast cancer, mutated *PIK3CA* activates 5-lipoxygenase through STAT3 activation. This results in high levels of leukotriene B4 (LTB4). LTB4 binds to LTB4 receptor type 2 on MDSC, causing infiltration into the carcinoma.⁸⁴ A targeted therapy blocking the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α -5-lipoxygenase-LTB4 axis prevented MDSC infiltration. In combination with immune checkpoint inhibition, this may provide new treatment avenues. In another report, the effect of lactate and the function of adenosine monophosphate-activated protein kinase (AMPK) α have been discussed.⁸⁵ Lactate, which is formed in hypoxic conditions, impairs the function of NK cells. The metabolite prostaglandin E1 (PGE2) also inhibits TH1 activation and differentiation, as well as the function of B cells. The transformation of macrophages M0 into M2 is facilitated by these metabolites. In contrast, AMPK can enhance the activity and infiltration of CD8⁺ T cells, improving the immunotherapeutic treatment. AMPK can also phosphorylate PD-L1 at Ser283, resulting in its degradation. AMPK agonists can also enhance the efficacy of anti-CTLA4 therapy. However, pro-tumor activities are also reported. As AMPK has various functions in metabolic programming, further studies may elucidate its functions and eventually enable its use in immunotherapy.

Autophagy is another mechanism associated with immune cell modulation, although its mechanism is not fully understood. Autophagy is observed in various types of lung cancer. The increase of autophagy in cancer cells liberates nutrients, decreases the formation of reactive oxygen species, and promotes the clearance of misfolded proteins. This provides a survival advantage for cancer cells in the tumor MEV. However, immune cells also infiltrate the MEV and encounter hypoxia, resulting in hypoxia-induced autophagy. Due to the crucial role of autophagy in immune cell proliferation as well as antigen presentation and T cell-mediated killing of tumor cells, anticancer treatment strategies based on autophagy modulation will need to consider the impact of autophagy on the immune system.⁸⁶ It has been shown that hypoxia leads to instability of gap-junctional connexin 43 and impairs melanoma cell death by NK cells in melanoma. Inhibition of autophagy

through pharmacological approaches may restore NK cell-mediated lysis of hypoxic melanoma cells.⁸⁷

Fibroblasts play a crucial role in the MEV, existing in various forms that are often conflated in the literature. The term cancer-associated fibroblasts refers to myofibroblasts. However, there are transitions; fibrocytes are usually stationary and stabilize the stroma. Upon activation to synthesize collagens and elastins, they transform into fibroblasts. If repair or modification of the matrix proteins is needed, they transform into myofibroblasts, which enables migration. In squamous cell carcinomas, they form the desmoplastic stroma reaction, which is the area of invasion. This is less common in adenocarcinomas. Fibroblasts assist tumor invasion by remodeling matrix proteins and favoring the formation of immature collagens. In contrast, by depositing elastin, they inhibit cancer cell invasion. The expression of aldo-keto reductases, glutathione S-transferases, and aldehyde dehydrogenase, often observed in squamous cell carcinomas, is associated with immunotherapy resistance.⁸⁸

4. Metabolic reprogramming

Tryptophan (Trp) and arginine (Arg) are well-known for their resistance mechanisms in the immunotherapy

of carcinomas. They will inhibit immunotherapy if their concentration in MEV is sufficiently high. Trp is catabolized by trp-2,3-dioxygenase or by indolamine-2,3-dioxygenase to kynurenine and picolinic acid, respectively (Figure 4). Macrophages metabolize Arg in two different ways. Nitric oxide synthase of M1 macrophages metabolizes Arg into nitric oxide and citrulline, whereas M2 macrophages use arginase to produce ornithine and urea from Arg. These metabolites inhibit the function of T cells and NK cells.⁸⁹ When arginase is blocked, tumor growth can be inhibited in combination with standard chemotherapy.⁹⁰ Besides, Arg also induces immunotolerance of Tcyt. Another factor associated with resistance and tolerance is adenosine. Ectonucleotidases CD73 and CD38 convert adenosine triphosphate (ATP) first to adenosine diphosphate (ADP), then further to AMP, from which adenosine is formed (Figure 5). These enzymes can be expressed by carcinoma cells and macrophages.⁹¹⁻⁹⁷ All these amino acids and the converting enzymes are part of the immune machinery in inflammation. These mechanisms are most likely involved in immune reactions in both the inflamed and excluded types. Interfering with these mechanisms is challenging. As all these amino acids are required for T-cell proliferation and multiplication, a blockade might also have negative

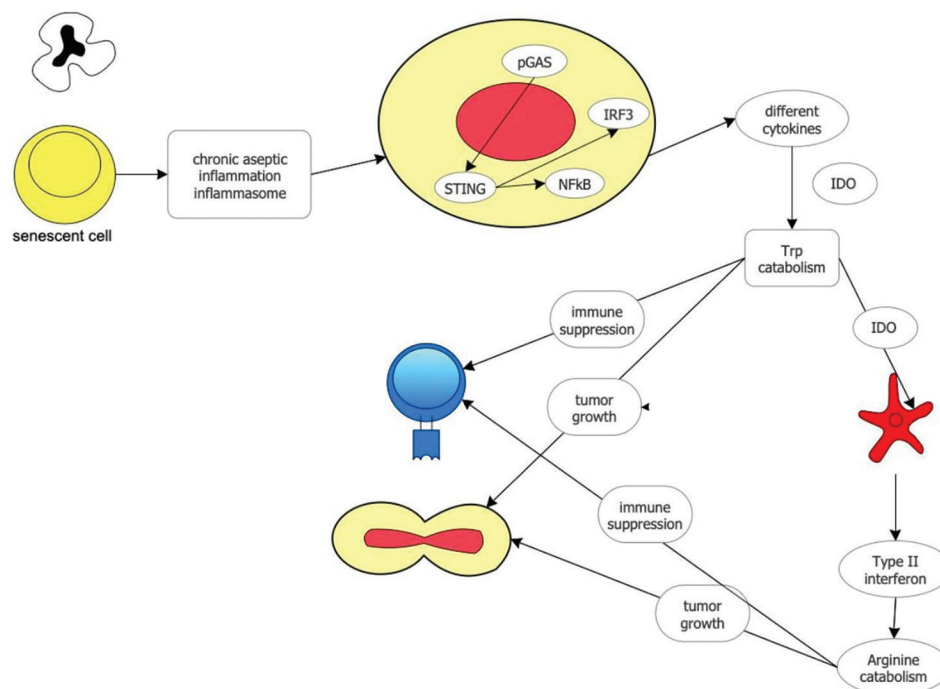


Figure 4. Scheme of the interaction of tryptophan and arginine and the immune reaction towards tumor cells. Senescence, often observed in tumor cells, produces a strong inflammatory signal, resulting in the secretion of cytokines. These will directly or indirectly cause metabolic activation of tryptophan and arginine, which induce a tolerance signal for T lymphocytes. Image created by the authors using ConceptDraw.

Abbreviations: cGAS: Cyclic guanosine monophosphate-adenosine monophosphate synthase; IDO: Indoleamine 2,3-dioxygenase; IRF3: Interferon regulatory factor 3; NFkB: Nuclear factor kappa B; STING: Stimulator of interferon genes.

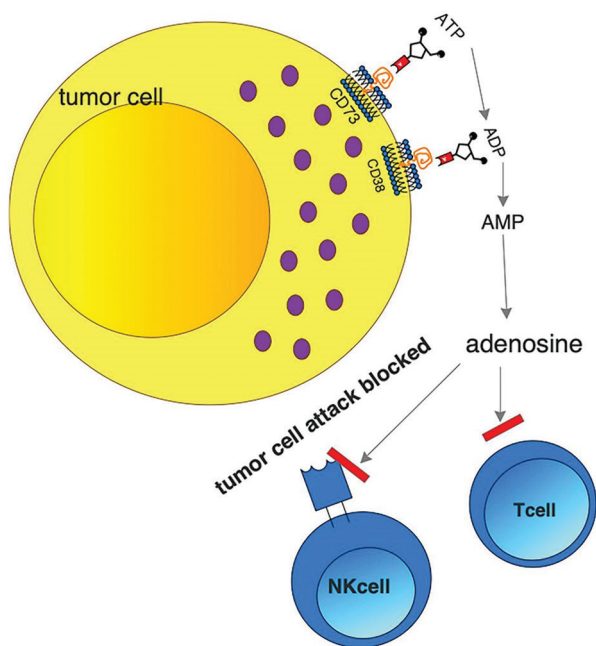


Figure 5. Mechanism of adenosine accumulation within the tumor microenvironment. The enzymes CD73 and CD38 are expressed on the cell membrane of macrophages or tumors. ATP is dephosphorylated to ADP by CD73, and CD38 creates AMP out of ADP. AMP is further cleaved to adenosine within the cytosol, which inhibits T cells and NK cells. Image created by the author using ConceptDraw.

Abbreviations: ADP: Adenosine diphosphate; AMP: Adenosine monophosphate; ATP: Adenosine triphosphate; NK: Natural killer.

effects by blocking cell divisions in these lymphocytes. Additionally, tumor cells require ATP for their metabolism and growth. However, the mechanism remains unknown.

A similar situation exists with adenosine, which accumulates in hypoxic tissues. NK cells are inactivated by adenosine through different mechanisms, including the inhibition of cytolytic activity, the suppression of cytotoxic granule expression, and the reduction of IFN- γ release.⁹⁸ Receptors for adenosine are expressed on various immune cells, and binding of adenosine suppresses pro-inflammatory effects. The interaction between adenosine and the receptors upregulates anti-inflammatory molecules and activates immunoregulatory cells, resulting in a long-lasting immunosuppressive environment.⁹⁹ Treatment has been focused on inhibiting the action of CD73 and CD38. However, CD38 could not be blocked, and the CD73 inhibitor, oclumab, influences myeloid and lymphocyte infiltrations into the MEV. Particularly, an increased number of CD8⁺ lymphocytes and activated macrophages was achieved.¹⁰⁰ These effects were further enhanced by combination therapy with anti-PD-1/PD-L1. The rationale for inhibiting the CD73-CD38-Arg system was further confirmed by elevated concentrations of ATP and ADP in bronchoalveolar lavage (BAL) fluid from cancer patients,

especially with metastases. Finally, a study blocking the adenosine A2A receptor, together with anti-PD-1, was effective in treating metastatic and residual disease.¹⁰⁰⁻¹⁰³ The function of adenosine receptors was investigated in NK cells. NK cells require antigen stimulation with signals from costimulatory OX40 or GITR. Blocking A2A and A2B receptors both decreased NK cell proliferation, whereas the opposite effect was achieved by blocking CD73. NK cells are also stimulated by Fms-like tyrosine kinase3-ligand, granulocyte-macrophage colony-stimulating factor, IL-2, and IL-15.¹⁰⁴

In a recent review, several aspects of metabolic influences on response or resistance to immunotherapy have been summarized, and the different functions of amino acids, as well as metabolites, have been discussed.¹⁰⁵ Glycolysis was shown to be important for the differentiation of macrophages, as M1 relies on glycolysis, whereas the shift to M2 is induced under glucose deprivation. M2 differentiation is further supported by glutamine, and under this condition, MDSCs are also reprogrammed into a pro-inflammatory phenotype. The polarization of M2 macrophages induces the expression of several genes, including *HIF1 α* , which further promotes the expression of immunosuppressive genes, such as *PD-L1*, *IL-10*, *CTLA4*, *LAG3*, and *TIM3*.¹⁰⁵

High lactate concentration, which occurs in hypoxic conditions and is common in lung cancer, especially in later stages, impairs T-cell proliferation. In contrast to cytotoxic T cells, Treg functions under low-glucose conditions. Arg regulates T-cell metabolism from glycolysis to oxidative phosphorylation, which promotes anti-tumor activity. The amino acid asparagine also induces activation of CD8⁺ T cells by binding to lymphocyte-specific protein tyrosine kinase. However, asparagine, as well as another amino acid, methionine (Met), are both depleted in lung carcinomas. A deficiency of Met causes reduced production of cytokines, S-adenosylmethionine, and H3K79 dimethylation by T cells, which downregulates STAT5 transcription. Trp depletion arrests T cells within the cell cycle and induces apoptosis. Kynurenine induces T-cell apoptosis and, in addition, promotes the generation of Treg. It also recruits and activates MDSC. A novel therapeutic option for immune-desert carcinomas was recently discussed.

Tertiary lymph follicles (TLF) are formed in some carcinomas (Figure 6). These TLFs are structured into a CD3-rich T-cell zone—where LAMP3⁺ DCs are found—and a CD20⁺ B lymphocytes-rich follicular zone with mature DCs. Such TLFs can be experimentally induced by C-X-C motif chemokine ligand (CXCL) 13 and IL-17. This stimulation will recruit lymphoid tissue. An addition

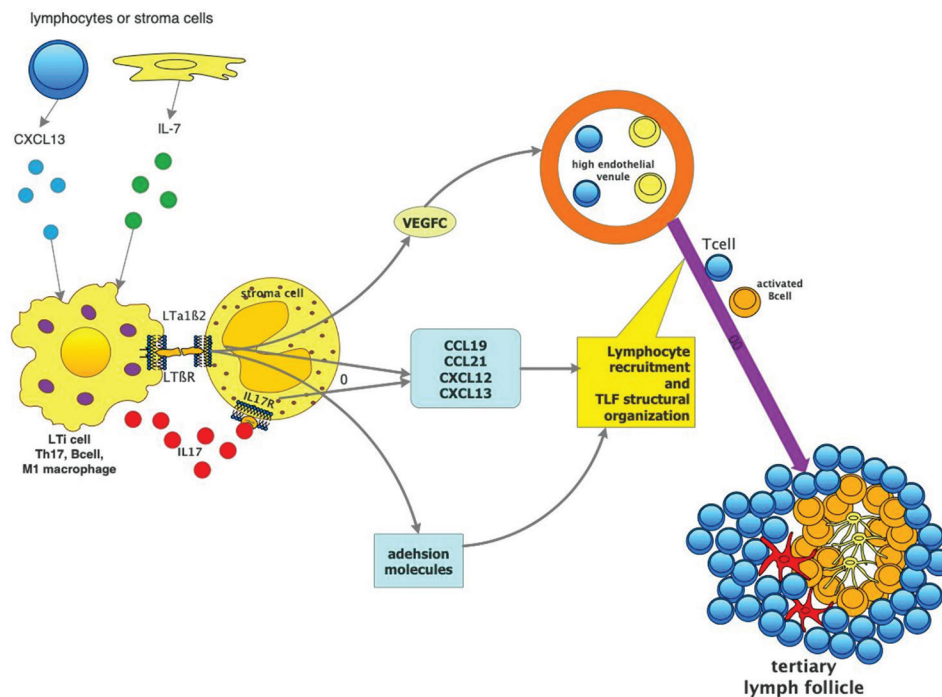


Figure 6. Mechanism of tertiary lymph follicles formation. Either lymphocytes or stroma cells secrete CXCL13 or IL-7, which act on stroma cells, TH17, B cells, or M1 macrophages, respectively. The transformation/activation of stroma cells is induced by the interaction of lymphotoxin $\alpha 1\beta 2$ and lymphotoxin β -receptor, resulting in IL-17-receptor expression, and the stroma cells are further stimulated by IL-17. This results in the secretion of vascular endothelial growth factor C, which induces the formation of high endothelial venules. These stroma cells also release CCL19, CCL21, CXCL12, and CXCL13. These chemokines recruit lymphocytes and activate B cells to form the TLF, inducing structural organization of the TLF (with orange indicating B cells, blue indicating T cells, and yellow or red indicating dendritic cells). This mechanism might be used for therapeutic interventions in immune desert-type tumors. Image created by the author using ConceptDraw.

Abbreviations: CCL: C-C motif chemokine ligand; CXCL: C-X-C motif chemokine ligand; IL: Interleukin; LT: Lymphotoxin; TH: T helper; TLF: Tertiary lymphoid follicle.

of B cells and M1 macrophages can enhance this effect. If stroma cells are stimulated by lymphotoxin $\alpha 1\beta 2$, the binding of lymphotoxin $\alpha 1\beta 2$ to receptor β induces the release of vascular endothelial growth factor C (VEGFC). VEGFC causes the formation of high endothelial venules, and these endothelial cells secrete vascular cell adhesion molecule 1 or mucosal addressin cell adhesion molecule 1 (Figure 6). This will cause lymphocytes to emigrate from the circulation and populate these TLFs. Trials are ongoing to simulate this experimental design using a mixture of cytokines.^{106,107} However, there are some caveats. Instillation of cytokine mixtures might induce a cytokine storm, which could prevent a positive therapeutic effect.

Another approach is the sequential combination of chemotherapy or radiotherapy, which can create TLFs, followed by the application of PD-L1 therapy combined with either LAG3 or TIM3.^{106,108} This strategy aims to produce multiple neoantigens from dying tumor cells to be presented to T lymphocytes. Additionally, the inhibition of the prostaglandin system has also been explored as a potential strategy to enhance anti-tumor immunity. Cyclooxygenase 2 (COX2) and PGE2 inhibit the maturation of DC and activation of NK and T cells, and promote differentiation of macrophages toward the M2 type. Inhibition of COX2 has shown some benefit in cancer therapy.¹⁰⁹

A novel approach targeting the immune system is the chimeric antigen receptor (CAR) technology. A fusion molecule is produced from a neoantigen with a fragment of the TCR. This fusion molecule is expanded in patients' lymphocytes. These antigen-primed cells are then reinfused into the patient. This was effectively applied in B-cell lymphomas. However, severe cytotoxicity (cytokine release syndrome) was seen when this therapy was applied in solid tumors.^{110,111} Further progress was made by combining CAR T-cell therapy with the gene editing system clustered regularly interspaced short palindromic repeats/Cas.¹¹² Instead of modified lymphocytes, the focus shifted to NK cells and macrophages. These cells could also be modified to detect neoantigens from cancer cells and attack them. This therapy has less toxicity, less cytokine release, and less neurotoxicity.¹¹³⁻¹¹⁶ NK cells could be harvested from pluripotent stem cells, and macrophages could be polarized to the M1 type. However, there are several challenges to this therapy, such as being time-consuming, requiring tedious lab work, and being costly.

A recent focus was drawn to phagocytosis. Phagocytosis is essential for macrophages and antigen-presenting cells. A neoantigen needs to be phagocytosed to be processed. The “do-not-eat-me signals,” which support cancer development and progression, were reported. This “do-not-eat-me” signal involves CD24 binding to sialic acid-binding Ig-like lectin 10 (Siglec10). This signal blocks innate immune cells, especially macrophages. A blockade of the CD24-Siglec10 binding decreased tumor growth.¹¹⁷ Thus, another potential approach for cancer immunotherapy has been discovered. Interestingly, this is not the only checkpoint of phagocytosis. Feng *et al.*¹¹⁸ described a phagocytosis checkpoint, namely the CD47-signal regulatory protein α (SIRP α) axis, another inhibitor of phagocytosis (Figure 7). When a CD47 antibody disrupts the CD47-SIRP α axis, phagocytosis is increased and tumor progression is inhibited. Under this treatment, an increase in M1 macrophages was observed. This treatment approach is currently being tested in combination with PD-L1.

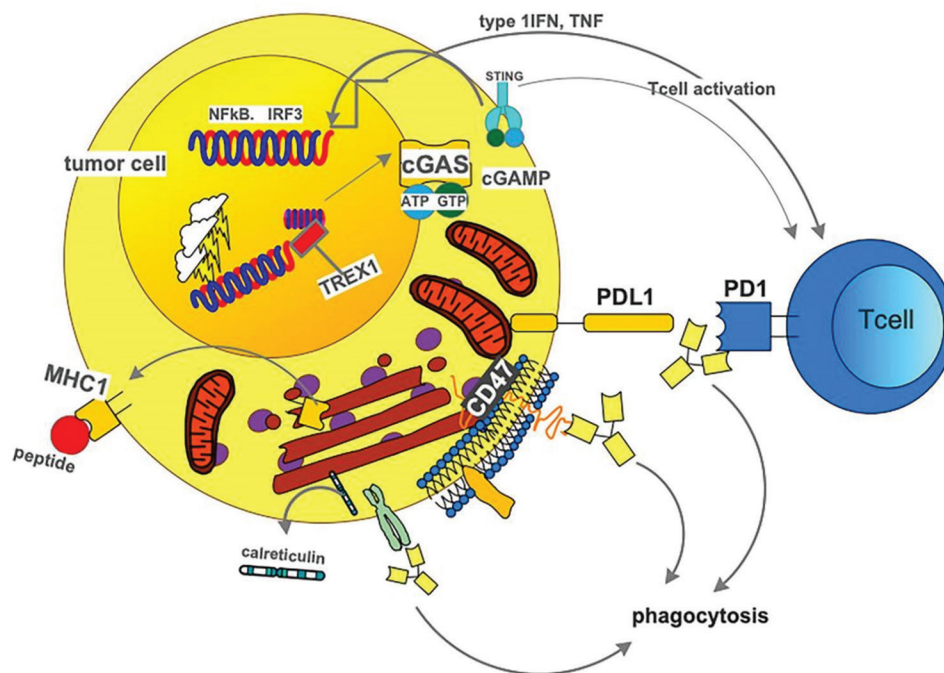


Figure 7. Combination therapy using phagocytosis checkpoint blockade with “do-not eat me” and “eat me” signaling. An irradiated (or chemotherapy-applied) tumor cell is shown, in which the treatment induces the release of calreticulin from the endoplasmic reticulum. There, it can synergize with CD47 blockade (an antibody against CD47). Radiotherapy or chemotherapy can also induce double-stranded DNA breaks, resulting in fragments within the cytosol. If not degraded by TREX1, this results in activation of cGAS-STING. STING mediates type 1 IFN response. This induces the release of pro-inflammatory cytokines, such as TNF. TNF promotes CD47 expression and sensitizes the tumor cell to CD47 blockade. Finally, the phagocytosis of PD-L1 by macrophages is inhibited. Therefore, the combined blockade of PD-1/PD-L1 and CD47 by antibodies may not only enhance phagocytic clearance of tumor cells but also improve anti-tumor T cell reaction. Image created by the author using ConceptDraw.

Abbreviations: ATP: Adenosine triphosphate; cGAS: Cyclic GMP-AMP synthase; cGAMP: Cyclic GMP-AMP; GTP: Guanosine triphosphate; IFN: Interferon; IRF3: Interferon regulatory factor 3; NFkB: Nuclear factor kappa B; PD: Programmed death; PDL: Programmed death ligand; STING: Stimulator of interferon genes; TNF: Tumor necrosis factor; TREX1: Tree-prime repair exonuclease.

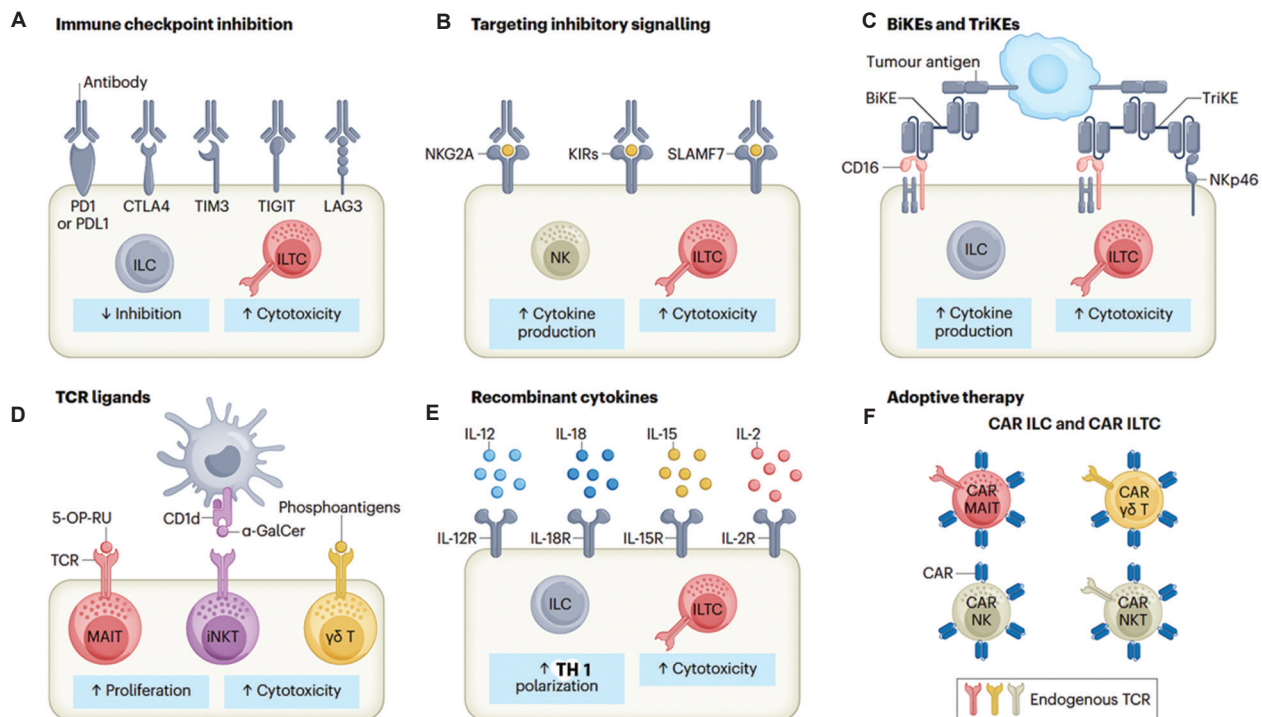


Figure 8. Summary of various resistance mechanisms. (A) Checkpoint inhibition. (B) Inhibitory signals. (C) Processing and recognition of antigens. (D) TCR and TCR ligands. (E) Effects of cytokines. (F) Adoptive therapy. Image created by the author using ConceptDraw.

Abbreviations: 5-OP-RU: 5-oxoprolinyl-uridine; α -GalCer: α -Galactosylceramide; BiKE: Bifunctional killer engager; CAR: Chimeric antigen receptor; CTLA4: Cytotoxic T-lymphocyte antigen 4; IL: Interleukin; ILC: Innate lymphoid cells; ILTC: Innate lymphoid tissue cells; iNKT: Invariant natural killer T cells; KIRs: Killer immunoglobulin-like receptors; LAG3: Lymphocyte activation gene 3; MAIT: Mucosal-associated invariant T cells; NK: Natural killer; NKG2A: Natural killer group 2 member A; NKp46: Natural killer cell protein 46; NKT: Natural killer T cells; PD: Programmed death; PDL: Programmed death ligand; SLAMF7: Signaling lymphocytic activation molecule family member 7; TCR: T-cell receptor; TH: T helper; TIGIT: T-cell immunoreceptor with Ig and immunoreceptor tyrosine-based inhibitory motif domains; TIM3: T-cell immunoglobulin and mucin domain-3; TriKE: Trifunctional killer engager.

As mentioned above, the role of DCs is becoming important in overcoming resistance to immunotherapy. A vaccination with CXCL9- and CXCL10-engineered DCs has led to enhanced T-cell infiltration and tumor inhibition in murine NSCLC models.¹¹⁹ This strategy has already led to a Phase I clinical trial.¹²⁰ For a long time, BAL was used in the evaluation of lung inflammatory diseases. BAL cells are washed out of the lung lobes affected by an inflammatory/immune disease. Lymphocyte typing enables the investigation of disease activity, the impact of therapy, and the diagnosis of certain diseases.¹²¹⁻¹²⁵ In lung tumors, BAL is often used to collect tumor cells from peripheral tumors, which are not otherwise accessible. Additionally, this tool can also be used to analyze the percentages of immune cells in lung lobes bearing lung carcinomas or molecules associated with immune reactions.

Response to immunotherapy cannot be assessed with any of the present-day markers. Neither PD-L1 nor tumor MTB can predict response with certainty. Expression of different modulators of immune responses, such as CD73, CD38, CD24, CD47, and others, can be evaluated

on tumor cells, immune cells, or as soluble markers in BAL. HLA diversity associated with response/resistance should be included in the tests, as well as the analysis of the tumor MEV with infiltrating Treg, CD8 T cells, neoantigen diversity, and clonal/subclonal neoantigen diversity.^{23,29} The field of tumor immunology is rapidly evolving, and our understanding of the complex mechanisms governing tumor-immune system interactions remains in its early stages.¹²⁶ In Figure 8, the different aspects of overcoming resistance in immunotherapy are summarized.

5. Conclusion

Immunotherapy of lung cancer is a rapidly expanding field. The increase in knowledge of immune and immune escape mechanisms has resulted in several new clinical trials. New checkpoint molecules are being tested, and the compositions of the cellular and molecular environment within the carcinoma are being explored. Additionally, novel drugs are being developed to influence the MEV to respond against the carcinoma cells.

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Conflict of interest

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Author contribution

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Consent for publication

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