Mechanisms of Resistance to Cancer Immunotherapy

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Abstract: Cancer immunotherapy has taken center stage in recent years as it can elicit a long-lasting anti-cancer response. However, the response rates are not consistently high in every patient. The majority of cancers still develop resistance to immunotherapy ranging from tumor intrinsic, microenvironment associated or host-related pathways. These include aberrant neoantigen presentation/processing, over-activation of tumor-cell-intrinsic signaling pathways, aberrant epigenetic regulation, presence of immunosuppressive cells, cytokines and chemokines, overexpression of multiple immune checkpoints and composition of gut bacteria. This review will focus on understanding the resistance mechanisms to immunotherapy in cancer and discuss ways to overcome this.

1 INTRODUCTION

Cancer immunotherapy utilizes or reactivates the patient's immune system, especially their T cells, to kill cancer cells. Meanwhile, it exerts a long-lasting anti-cancer response on the human body, which is unmatched compared to other therapies (Ribas & Wolchok, 2018). As evidence shows, blocking PD-1/PD-L1 or CTLA-4 pathways can induce long-lasting remission of cancers including melanoma, urothelial cancer, head and neck squamous cell carcinoma (HNSCC), lung cancer and renal cell carcinoma (RCC). These therapies have also obtained FDA approvals (Gong et al., 2018). Additional to the PD-1/PD-L1/CTLA-4 immunotherapies, several other targeted immunotherapy options range from chimeric antigen receptor-modified T cells (CAR-T cell) therapy, cancer vaccines, and oncolytic viruses, which have shown positive results clinically and pre-clinically. For example, the CAR-T cell therapy for B cell malignancies has been proven effective and safe, especially one of which targeting CD19 reached an overall survival rate of 78% (Maude et al., 2014).

Although cancer immunotherapy has been widely and rapidly applied to treat various types of cancer, only a few patients (responders) have benefited from them due to the complexity of immune systems. Many patients do not produce any clinical benefit (non-responders/ innate resistance) after immunotherapy. For example, tumors that have limited T cells in the tumor microenvironment (TME), called immune cold or immune-desert cancers such as prostate cancer, have had minimal benefit from immunotherapy (Galon & Bruni, 2019; Hegde et al., 2016). This form of innate resistance can also be seen in glioblastoma and breast cancer, which have low objective response rates with the anti- PD-1/PD-L1 therapy (Dirix et al., 2018; Hansen et al., 2018; Lukas et al., 2018). Additionally, some patients first respond to immunotherapy but subsequently develop acquired resistance (Jenkins et al., 2018). Therefore, it is vitally important to determine the mechanism through which cancers regulate immunotherapy resistance.

The resistance mechanisms to cancer immunotherapy are divided into three parts, tumor-cell-intrinsic mechanism, TME-related mechanism, and host-related mechanism. The tumor-cell-intrinsic mechanism includes the alteration of neoantigen, tumor cell signaling pathway and epigenetic regulation. The TME-related mechanism involves immunosuppressive cells, cytokines, chemokines and multiple immune regulators. Finally, the host-related mechanism is associated with patients' gender, age and gut bacteria. This review will concentrate on the mechanisms of resistance to cancer immunotherapy

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from these three parts above and discuss ways to overcome immunotherapy resistance.

2 TUMOR-CELL INTRINSIC MECHANISM

2.1 Alteration of Neoantigen

Though cancers have been known to be infiltrated by antigen-specific CD8+ cytotoxic immune cells, they often do not elicit an immune response. The ability of cancers to initiate an adaptive immune response depends on the presentation of neoantigenic peptides by the cancer cell and their subsequent recognition by cytotoxic cells (Reeves & James, 2017; Snyder et al., 2014). A high tumor mutational burden (TMB), denoted by increased mutations within a cancer cell, usually accompanies the production of increased neoantigens by cancer (Hugo et al., 2017; Perumal et al., 2020; Rizvi et al., 2015; Schumacher & Schreiber, 2015). This indicates higher immunogenicity within the tumor and immunotherapy targeting these tumors have produced a favorable response. However, cancers have the ability to alter the expression of and presentation of neoantigens to aid in immune escape (Veldman et al., 2020) (Figure 1).

High TMB cancers such as non-small cell lung cancer (NSCLC) and melanoma produce increased neoantigens, resulting in a favorable response to anti-PD-1/PD-L1 therapy (Goodman et al., 2017b). By contrast, tumors such as prostate cancer with low TMB, which lack neoantigens, are less sensitive to immunotherapy (Schumacher & Schreiber, 2015). Additionally, Hellmann et al. found that high TMB positively correlated to an immunotherapy response, durable benefit, and progression-free survival with immune checkpoint blockade treatment (Hellmann et al., 2018). However, several studies have pointed out that the clinical efficacy of immunotherapy does not strongly depend on high TMB alone (Goodman et al., 2017a; Gromeier et al., 2021; Strickler et al., 2021). For example, patients with glioblastoma, a low TMB cancer, had favorable survival responses to immunotherapy (Gromeier et al., 2021).

Studies have also found that epigenetic changes resulting in loss of neoantigen expression can aid cancers to evade immune surveillance (De Vries et al., 1997). For example, hypermethylation of the promoter of neoantigen expressing genes during transcription resulted in neoantigen silencing (Rosenthal et al., 2020).

Abnormal antigen processing can lead to errors in antigen presentation, impairing cytotoxic CD8+ T cells to recognize the antigen, leading to immune escape. In general, neoantigenic peptides are processed into antigenic peptides by the proteasome together with low molecular mass proteins (LMP). Processed peptides are transported into the endoplasmic reticulum (ER) via the transporter associated with antigen processing proteins (TAP) and assembled with human leukocyte antigen (HLA) and Beta-2-Microglobulin (B2M) to form the major histocompatibility complex class 1 (MHC-1). These complexes are then transported on the tumor cell surface, which aids in T cell recognition (SELIGER et al., 1997). Naturally, all of these steps are indispensable for the presentation of neoantigens. In cancer patients, loss and down-regulation of LMP2, LMP7 and TAP1 were reported, resulting in the failure of presentation of neoantigens (Meissner et al., 2005). The expression rates of LMP2, LMP7, TAP1, TAP2, and HLA were also found to predict the overall survival of cancer immunotherapy (Meissner et al., 2005). Studies have found that loss of heterozygosity and loss of function of the HLA gene, which is one of the mechanisms causing immune evasion (Mcgranahan et al., 2017). After treatment with an RNA mutanome vaccine, B2M-deficient patients with melanoma lacking presentation of neoantigens had increased tumor growth, leading to recurrence, indicating that this is also one of the resistance mechanisms to immunotherapy (Sahin et al., 2017). Tumor cell division can produce new mutant subclones leading to intratumoral heterogeneity. The selective pressure by immune sculpting can result in the expansion of subclones that lack neoantigens or down-regulate their genes in presentation machinery, aiding cancer growth and reducing the effect of immunotherapy (Mcgranahan et al., 2016).

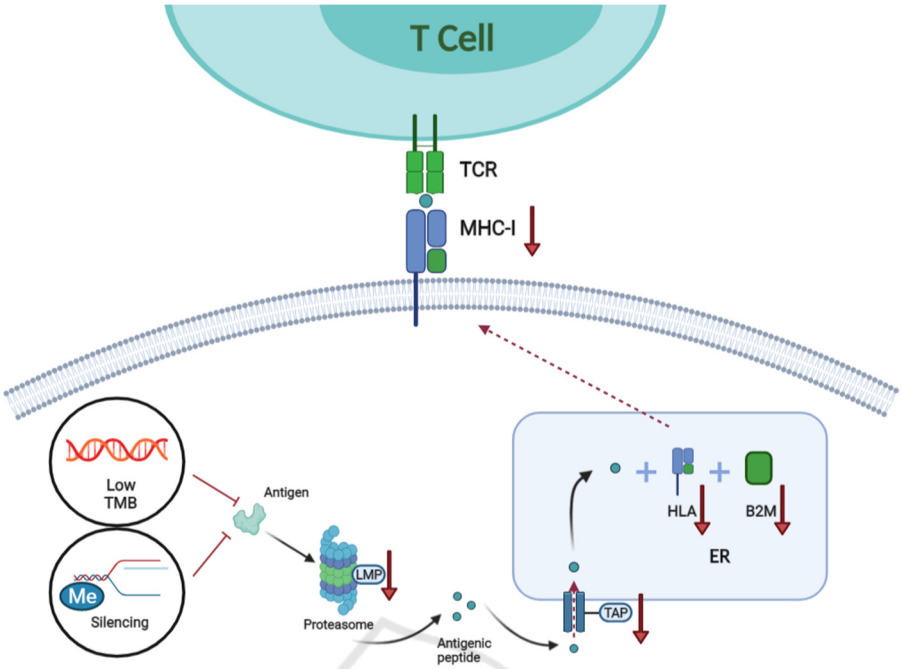

Figure 1: Neoantigen-related mechanism of resistance to immunotherapy.

Tumor mutation generates tumor-specific peptides or neo-antigenic peptides. Peptides produced are processed into antigenic peptides by the proteasome where the LMP is involved. Next, the antigenic peptides are transported into the ER, where they are loaded onto the MHC class 1 complex which consists of HLA-A, B, C and B2M. Finally, MHC is transported and displayed on the tumor cell surface and recognized by the TCR of T cells. Lack of neoantigen due to low TMB, loss of neoantigen due to the silencing of neoantigen (such as methylation) and disruption in antigen presentation machinery (such as the abnormal expression of LMP, TAP, HLA and B2M) can result in immunotherapy resistance.

2.2 Epigenetic Regulation of Antigen Presentation and Recognition Pathway

Aberrant epigenetic regulation has been reported to mediate various tumor-related genes, induce tumor progression and metastasis and promote immunotherapy resistance (Baylin & Jones, 2016; Maio et al., 2015). Epigenetic regulation can also suppress the expression and presentation of tumor-associated antigens through processes like DNA methylation, acetylation and histone modification (Cao & Yan, 2020). In tumors resistant to immunotherapy, down-regulation of immunogenic antigens through DNA methylation has been reported and DNA demethylating agents could restore the expression of neoantigens (Wylie et al., 2019). As mentioned above, HLA, TAP and B2M are involved in the antigen presentation machinery. The promoter region of the HLA gene has been reported to be methylated, inhibiting its expression and resulting in an impaired CD8+ T cell response (Luo et al., 2018). Methylation was also observed in the promoter region of B2M (Snahnicanova et al., 2020). Similarly, reduced recruitment of histone acetyltransferase to TAP-1 promoter regions was linked to its reduced transcription, leading to dysfunctional antigen presentation (Setiadi et al., 2007). This imbalance in proteins involved in antigen presentation via epigenetic regulations can result in a lack of immunogenic antigens, resulting in resistance to immunotherapy.

The function of T cells is also regulated by epigenetic modification. For instance, PD-1, CTLA-4, lymphocyte-activation gene 3 (LAG-3), and T cell immunoglobulin domain and mucin domain 3 (TIM-3), were demethylated or hypomethylated leading to T-cell exhaustion (Sasidharan Nair et al., 2018). Furthermore, the enhancer of zeste homologue 2 (EZH2) induced H3 trimethylation and DNA methyltransferase 1 (DNMT1) induced DNA methylation, leading to a decrease in the expression of chemokines CXCL9 and CXCL10, important for T

helper cell recruitment into the tumor stroma (Nagarsheth et al., 2016; D. Peng et al., 2015).

Cancer cells also have the ability to prevent T cell-induced apoptosis by regulating cell-extrinsic apoptotic pathways through epigenetic regulation. The binding of Fas-L on the CD8+ lymphocytes with its counterpart FAS on the tumor cell can trigger apoptosis of the cancer cell. However, cancers can downregulate the expression of Fas and TRAIL-R1 proteins by DNA methylation, preventing CD8+ induced apoptosis (Hopkins-Donaldson et al., 2003). Similarly, histone deacetylation has also been implicated in silencing TRAIL and Fas signaling pathways (Insinga et al., 2005).

Epigenetic induced immunotherapy resistance can be overcome by combining immunotherapy with drugs targeting epigenetic modifications, and this combination has produced favorable outcomes in recent clinical trials (Gallagher et al., 2017; Pauken et al., 2016). For example, histone deacetylase inhibitor (HDACi) can overcome the resistance to monoclonal anti-CD52 antibody (alemtuzumab) in patients with T-cell prolymphocytic leukemia (Hasanali et al., 2015). Likewise, DNA hypomethylating agents (DHAs) guadecitabine combined with anti-CTLA-4 antibody ipilimumab displayed promising tumor immunomodulation through the upregulation of HLA class I and increasing CD8+, PD-1+ T cells and CD20+ B cells in a phase Ib trial (Di Giacomo et al., 2019).

2.3 Tumor-Intrinsic Cell Signaling Pathway

Studies have shown that the alteration of various oncogenic cell signaling pathways can affect the immune response to tumors (Aldea et al., 2021; Kalbasi & Ribas, 2020). The changes may affect the expression of transcription factors, resulting in aberrant antigen presentation, expression of immune checkpoint-related proteins, or the production of immunosuppressive cytokines (Fares et al., 2019; W. Peng et al., 2016). It is also vital to note that the role of the tumor cell signaling pathway will have a context-dependent role in promoting immunosuppression.

2.3.1 Alteration of PI3k/AKT Signaling Pathway

The PI3K/AKT signaling network is activated via ligand binding to receptor tyrosine kinases (RTK), G protein-coupled receptors (GPCR), or cytokine receptors. This pathway plays a central role in promoting cell survival and growth (Hoxhaj & Manning, 2020). The proteins phosphatidyl-inositol-3-kinases (PI3Ks), protein kinase B (AKT), mammalian target of rapamycin (mTOR) and phosphatase and tensin homolog (PTEN) are involved in this signaling network. PTEN is the negative regulator of PI3k/AKT signaling netwpork, which inhibits PI3K and prevents AKT activation (Porta et al., 2014). Thus, loss of *PTEN* induces abnormally activation of the PI3k/AKT signaling pathway (Porta et al., 2014).

The expression of PD-L1, one of the immune checkpoint inhibitory receptors, has been reported to be controlled by the PI3K-AKT-mTOR pathway. Membranous expression of PD-L1 is positively correlated with the activation of mTOR, thereby reducing tumor-infiltrating T cells, increasing regulatory T cells (Tregs), and resulting in immune escape (Lastwika et al., 2016). Loss of PTEN has been shown to up-regulate immunosuppressive cytokines of CCL2 and VEGF, which can recruit tumor-associated macrophages (TAMs) and aid in immune escape (W. Peng et al., 2016; Voron et al., 2014; H. Yang et al., 2020). Additionally, increased VEGF can also cause abnormal angiogenesis. This potentiates the immunosuppressive phenotype by recruiting suppressive immune cells, such as Tregs and myeloid-derived suppressor cells (MDSCs), reported to promote resistance to immunotherapy in melanoma (W. Peng et al., 2016; Voron et al., 2014). Mutations in *PIK3CA* coding the p110 subunit of PI3K cause abnormal activation of the PI3K and can reduce immune infiltration (Borcoman et al., 2019; Madsen et al., 2018). Direct activation of the PI3k-AKT pathway through activating mutations can also lead to a suppressive tumor microenvironment. For example, *RHOA* mutations in gastric cancer (GC) can trigger the PI3K-AKT-mTOR pathway to increase the synthesis of free fatty acids (released by tumor cells), which promotes Treg cell metabolism, ultimately contributing to an increased Tregs in TME (Kumagai et al., 2020).

2.3.2 Alteration of ERK/MAPK Signaling Pathway

Similar to PI3K/AKT signaling pathway, mitogen-activated protein kinase (MAPK) signaling is activated when receptors such as RTKs and GPCRs bind to their ligand. Hyperactivation of this pathway results in cancer development and progression. The main proteins involved in this signaling pathway are RAS, RAF, MEK and ERK from upstream to downstream (Guo et al., 2020).

The expression of PD-L1 can be regulated by ERK/MAPK signaling pathway, and the activation of this pathway can also decrease the TILs (Loi et al., 2016; Sumimoto et al., 2016). Abnormal EGFR signaling via the MAPK pathway can up-regulate the expression of PD-L1 through the p-ERK1/2/p-c-Jun transcription factors, causing T cell apoptosis (Chen et al., 2015). The activation of RAS and its downstream signaling MEK can also indirectly promote PD-L1 expression by inhibiting AU-rich element-binding protein tristetraprolin (TTP) by kinase MK2 (Coelho et al., 2017). *KRAS* (one of *RAS* family members) mutation mediates the inhibition of interferon regulatory factor 2 (IRF2), leading to high expression of CXCL3 to form an immunosuppressive microenvironment (Liao et al., 2019). Furthermore, the eukaryotic translation initiation complex (eIF4F) located downstream of the PI3K-AKT and ERK-MAPK pathway regulates PD-L1 transcriptional factor STAT1, whose activation has a positive correlation with the activation of PD-L1 (Cerezo et al., 2018). Clinically, in patients who developed hyperprogressive disease following anti-PD-1 therapy, it was found to have over activation of the ERK/MAPK, PI3K/AKT, IGF-1 and TGF-b signaling pathways, suggesting their role in promoting immunotherapy acquired resistance (Xiong et al., 2018).

2.3.3 Alteration of Wnt/β-Catenin Signaling Pathway

Wnt/β-Catenin signaling pathway is activated upon Wnt ligand binding to Frizzled receptors. As a result, β-Catenin translocates into the nucleus and binds to transcription factors of target genes related to cancer progression (Zhang & Wang, 2020).

Studies have shown that the Wnt/β-catenin pathway may promote immunotherapy resistance by producing immunosuppressive cytokine IL-10 in melanoma (Yaguchi et al., 2012). Melanoma cells expressing β-catenin cannot produce C-C motif chemokine ligand (CCL4), causing defective recruitment of antigen-presenting CD103+ Dendritic Cells (DCs). This can lead to the loss of the chemokines derived by CD103+ DCs, such as CXC motif chemokine ligand 9 (CXCL9) and CXCL10, which reduce cytotoxic T lymphocytes (CTLs) tumor infiltration and damage the anti-tumor immune response (Spranger et al., 2015). Another example also reported that in non-T-cell-inflamed tumors, the activation of tumor-intrinsic WNT/β-catenin signaling reduced immune cell infiltration (Luke et al., 2019).

2.3.4 Alteration of Cell Signaling Pathways Related to IFN

Tumor intrinsic interferon (IFN) signaling pathway is activated via autocrine and paracrine IFNs binding onto its receptor (IFNGR1/IFNGR2) (Dunn et al., 2006; Reisländer et al., 2019). This mediates the transcription of interferon-stimulated genes through the JAK-STAT pathway, resulting in enhanced T cell response and the tumor cells' apoptosis (Ni & Lu, 2018; Reisländer et al., 2019). However, contrary to this, the IFN pathway has also been implicated in resistance to immunotherapy.

One mechanism of acquired resistance to anti-PD-1 immunotherapy has been linked to the mutation of JAK1/2. This mutation prevents activation of downstream IFN transcription factor, which impairs the transcription of interferon receptors, resulting in the lack of IFN receptors and decreasing the effect of IFN (Zaretsky et al., 2016). JAK1/2 loss of function mutation has also been shown to inhibit the expression of PD-L1 and the response to anti-PD-L1 therapy (Shin et al., 2017). Mutations of IFN-γ pathway genes, such as *IFNGR1, IFNGR2, IRF-1* and *JAK2*, also resulted in unfavorable responses to anti-CTLA-4 therapy, which could be a mechanism of resistance to immunotherapy (Gao et al., 2016). Interestingly, anti-CTLA-4 therapy can increase the interferon-γ response genes, including CTLA-4 through the JAK-STAT pathway, resulting in resistance to CTLA-4 (Mo et al., 2018). It is also shown that IFN-γ promoted PD-L1 expression resulting in immune evasion via the cell signaling pathway of JAK-STAT -IRF1 (Garcia-Diaz et al., 2017).

3 TUMOR-CELL EXTRINSIC MECHANISM

3.1 Immune Contexture of the Tumor Microenvironment

In addition to tumor-intrinsic resistance mechanisms, tumor TME also plays a vital role in causing resistance to cancer immunotherapy. The TME includes immunosuppressive cells, cytokines and chemokines, which could impair cytotoxic cells and the immune system (Galon & Bruni, 2019; Hegde et al., 2016). Additionally, some tumors have been reported to reduce the presence of T cells in the microenvironment, such as prostate cancer (Galon & Bruni, 2019; Hegde et al., 2016). The immune cell

composition within the tumor is also an essential factor that could predict response to immunotherapy.

The TME consists of cytotoxic cells such as CD8+ T cells, NK cells and DC cells that aid immune surveillance and cancer destruction. However, it also contains MDSCs, Tregs and M2 macrophages, which are immunosuppressive and induce immune system dysfunction and tumor immune escape, resulting in resistance to cancer immunotherapy (Aldea et al., 2021). In the TME, MDSCs are able to inhibit the proliferation and activity of CD8+ T cells and release immunosuppressive cytokines, promoting tumor proliferation and metastasis (Hou et al., 2020; Law et al., 2020). Tregs are immunosuppressive to aid immune homeostasis, but in tumors, they promote tumor progression as a suppressor of anti-tumor immunity via releasing immunosuppressive cytokines and binding to tumor cells or antigen-presenting cells (APCs), leading to T-cell exhaustion (Takeuchi & Nishikawa, 2016). Unlike the above two, Macrophages have a high degree of plasticity, which have been classified as M1 and M2 (Mosser & Edwards, 2008). M1 macrophages are involved in anti-tumor immunity, while M2 macrophages (also known as tumor-associated macrophages, TAMs) are related to the progression and metastasis of tumors and the formation of immunosuppressive TME (Italiani & Boraschi, 2014). And its immunosuppressive function is similar to MDSCs (Italiani & Boraschi, 2014).

In the clinic, MDSCs, Tregs and TAMs frequency were shown to be related to unfavorable prognosis and shorter overall survival (OS) in various types of cancer (Ai et al., 2018; Fridman et al., 2012). For example, patients developing resistance to anti-PD-1 therapy showed an increased expression of TIM-3 binding to galectin-9 on MDSCs when the treatment failed (Limagne et al., 2019).

Recently, there has been an influx in treatments targeting the composition of the immune microenvironment to prevent innate resistance to immunotherapy. Combination treatment with CTLA-4 and PD-L1 inhibitors has been reported to increase T cell infiltration in immune cold prostate cancer (Sharma et al., 2020). As mentioned above, TAMs can also promote tumor angiogenesis. Treatment with bispecific anti-ANG2/VEGF-A antibody (CrossMab, A2V) successfully improved the survival rate of vasculature-aberrant glioblastoma, owing to the reprogramming of TAMs from M2 to M1 (Kloepper et al., 2016). With the treatment of CD25-blocking monoclonal antibody daclizumab, Tregs lost the immunosuppressive function and restored the ability to generate interferon-γ (Rech et al., 2012).

3.2 Expression of Immune-Modulatory Factors

MDSCs, TAMs and Tregs are able to release cytokines within the TME, promoting tumor immune evasion (Haist et al., 2021). MDSCs can secrete interleukin-10 (IL-10), IL-17 and transforming growth factor-β (TGF-β). TAMs can also secrete TGF-β and IL-10. This results in suppressing CD8+ T-cell function and promotes the immunosuppressive function of Tregs (Huang et al., 2006; Wang et al., 2019; Z. Yang et al., 2010). The proliferation and the function of T cells can be inhibited by Tregs via secreting cytokines, such as IL-35, IL-10 and TGF-β (Jarnicki et al., 2006; Turnis et al., 2016). IL-35 can also promote multiple inhibitory receptors such as PD1, TIM-3, LAG-3 and cause T cell exhaustion (Turnis et al., 2016). Besides T cells, NK cells are also inhibited by the MDSCs secreting TGF-β1 (Li et al., 2009). TGF-β1, secreted by MDSCs, TAMs and Tregs, can also contribute to adaptive immunotherapy resistance to anti-PD1 therapy by restricting T cell infiltration (Mariathasan et al., 2018). Treatments co-targeting these chemokines with immunotherapy agents can prevent resistance and have shown clinical benefits. A combination of anti-CXCR2 (CXCR2 expressing by MDSCs) with anti-PD1 was shown to reduce tumor size and enhance T-cell infiltration (Najjar et al., 2017). The bifunctional agent (anti-PD-L1 and anti-TGFβ), Bintrafusp Alfa, enhanced tumor cell lysis and reduced Tregs activity (Lind et al., 2020).

3.3 Multiple Inhibitory Regulators

Immune checkpoints can regulate the activation of CD8+ T cells, of which the most common ones are PD-1 and CTLA-4. In addition to the two, there are more inhibitory regulators which can bind to the surface of tumor cells or APCs, leading to T-cell exhaustion. These include LAG-3, TIM-3, T cell immunoreceptor with Ig and ITIM domain (TIGIT), and V-type immunoglobulin domain-containing suppressor of T cell activation (VISTA) (Ding et al., 2020; Kurachi, 2019). Immune checkpoint treatments have shown to up-regulate secondary immune regulators that cause immunotherapy resistance (Nowicki et al., 2018). Therefore, the combination treatment with multiple immune regulators can enhance the effect of checkpoint blockade monotherapy (Long et al., 2018; Seidel et al., 2018). For example, the patients that showed no response to monotherapy of ipilimumab (anti-CTLA-4) benefited from a subsequent therapy of nivolumab (anti-PD-1)

in melanoma (Weber et al., 2013). There was also the case when combining an anti-PD-L1 agent with an anti-Tim-3 agent. Combination treatment reversed T cell exhaustion and reduced the tumor growth in colon carcinoma (Sakuishi et al., 2010). Combining multiple checkpoint inhibitors could be a promising strategy to overcome immunotherapy resistance.

3.4 Tumor Cell-Extrinsic Metabolic Pathway

The metabolic pathway around the TME also plays a vital role in promoting resistance to immunotherapy. It includes the pathway of glycolysis, the pathway of depleting various amino acids, and the production of adenosine. Cancer cells and surrounding immune cells undergo these metabolic reprogramming that can promote resistance to immunotherapy (Fares et al., 2019).

In 1926, Warburg proposed that tumor cells obtain energy through tumor-specific glycolysis, producing a large amount of lactic acid (Warburg, 1956; Warburg et al., 1927). Aberrant glycolysis results in the production of lactate and H^+, which are released by various H^+ transporters (such as monocarboxylate transporter 4, MCT4) into the extracellular matrix. This results in a lower extracellular pH (pH_e) and tumor acidosis (Corbet & Feron, 2017). Warburg effect in cancer cells can influence the immune response of immunotherapy partly via glucose competition, lactate production, and the creation of an acidic TME.

Studies have shown a glucose competition between tumor cells and T cells, which restricts T cell function by reducing their glycolytic capacity, cytolytic activity, cytokines production and IFN-γ production. This leads to T cell hyporesponsiveness and an impaired immune response (Cham et al., 2008; Chang et al., 2015). However, recent findings have suggested that MDSCs and TAMs have the highest glycolytic capacity, outcompeting the T cells for glucose over the cancer cells (Reinfeld et al., 2021). The resulting lactate produced from glycolysis was also shown to decrease the cytotoxic activity and the expression of granzyme and perforin in NK cells, suppressing their anti-tumor immune response (Husain et al., 2013). Additionally, a lower pH_e in TME causes the reduction of cytotoxic cytokines, such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (INF-γ) (Müller et al., 2000). This acidic condition has also been reported to promote macrophage polarization towards an immunosuppressive phenotype, TAM (Bohn et al., 2018).

Within the TME, there is also competition for the consumption of amino acids, such as tryptophan, cysteine, and arginine by the immunosuppressive cells. MDSCs can reduce the level of local tryptophan by expressing indoleamine 2,3 dioxygenase (IDO), causing the reduction of nutrients for T cells leading to their dysfunction (Yu et al., 2013). In murine models, the combination therapy of checkpoint inhibitors with IDO blockade can reactivate these dysfunctional T cells and restore their IL-2 production (Spranger et al., 2014). Additionally, MDSCs are also known to sequester essential amino acid cystine and reduce the availability of cysteine within the TME. Reduction in free cysteine can downregulate T cell activation as T cells cannot produce cysteine due to lack of cystathionase (GMÜNDER et al., 1991; Srivastava et al., 2010). L-arginine, which regulates the T-cell cycle progression, can also be depleted by MDSCs and TAMs through arginase I, further contributing to immunotherapy resistance (Barbul & Dawson, 2018; Munder et al., 2006; Rodriguez et al., 2007).

CD39 and CD73 are known to convert free ATP into adenosine which is released into the TME and can inhibit T cell function via its interaction with A2A receptors (A2AR) or A2B receptors (A2BR) on immune cells. This results in immune suppression via the increased expression of various immune checkpoints and decreased cytokine production (B. Allard et al., 2017; D. Allard et al., 2017; Cekic & Linden, 2016; Sek et al., 2018). Extracellular adenosine can promote CTLA-4 expression in Tregs and reduce IL-7 levels, which aids in the development and survival of naïve T cells (Cekic et al., 2013; Deaglio et al., 2007). The activation of A2BR can also promote the expansion of MDSCs (Ryzhov et al., 2011). Preclinically, it has shown that combinations of checkpoint inhibitors with A2AR blockade can inhibit adenosine and restore T cell function, and the combination with CD73 blockade can reduce the conversion of adenosine. Targeting the metabolic pathways in cancer can be a potential therapeutic strategy to overcome resistance to immunotherapy (B. Allard et al., 2013; Beavis et al., 2015).

4 HOST-RELATED MECHANISM OF RESISTANCE

Host-associated factors such as age, gender, and composition of intestinal bacteria may also affect the response to immunotherapy (Figure 2). It had been previously reported that aging could dampen the

function of the immune system, thereby affecting the efficacy of immunotherapy (Hong et al., 2019). However, a recent meta-analysis indicated no association between age and the effectiveness of immunotherapy (F. Yang et al., 2020). Similarly, several studies have also shown opposing results regarding the association between the efficacy of immunotherapy and gender (Wallis et al., 2019; F. Yang et al., 2020).

There is growing evidence suggesting that the host-microbiome has a role in modulating response to cancer immunotherapy. It was reported that the pathogen-associated molecular patterns (PAMPs) from the intestinal microbiome, such as lipopolysaccharide, could directly activate APCs such as DCs, which can translocate into mesentery lymph nodes (MLNs) to prime the B and T cells at distant sites (Stary et al., 2015). Additionally, the gut microbiomes are able to induce the secretion of immunomodulatory factors to regulate the immune system. For example, short-chain fatty acids (SCFAs) (such as pentanoate and butyrate) are microbial metabolites, which can increase cytokine production, such as TNF-α, CD25 and IFN-γ to enhance the anti-tumor function of T cells and CAR-T therapy (Luu et al., 2021). In germ-free (GF) mice, tumor progression was not controlled by anti-CTLA-4 therapy, while the GF mice fed with *B. uniformis* restored the responsiveness to anti-CTLA-4 therapy (Vétizou et al., 2015). As a result, the combination of immunotherapy and gut microbiome seems to be a promising strategy to overcome the resistance in the clinic. The treatment with *Bifidobacterium* can enhance anti-PD-L1 therapy in vivo, resulting in abolishing the growth of tumors via increasing expression of the genes involved in CD8+ T cell activation, antigen processing and presentation, and interferon signaling (Sivan et al., 2015). Furthermore, a higher microbial diversity with *Bifidobacterium longum, Collinsella aerofaciens, Enterococcus faecium, Ruminococcaceae, Clostridiales,* and *Faecalibacterium* is also associated with a better prognosis for checkpoint blockade therapy (Gopalakrishnan et al., 2018; Matson et al., 2018).

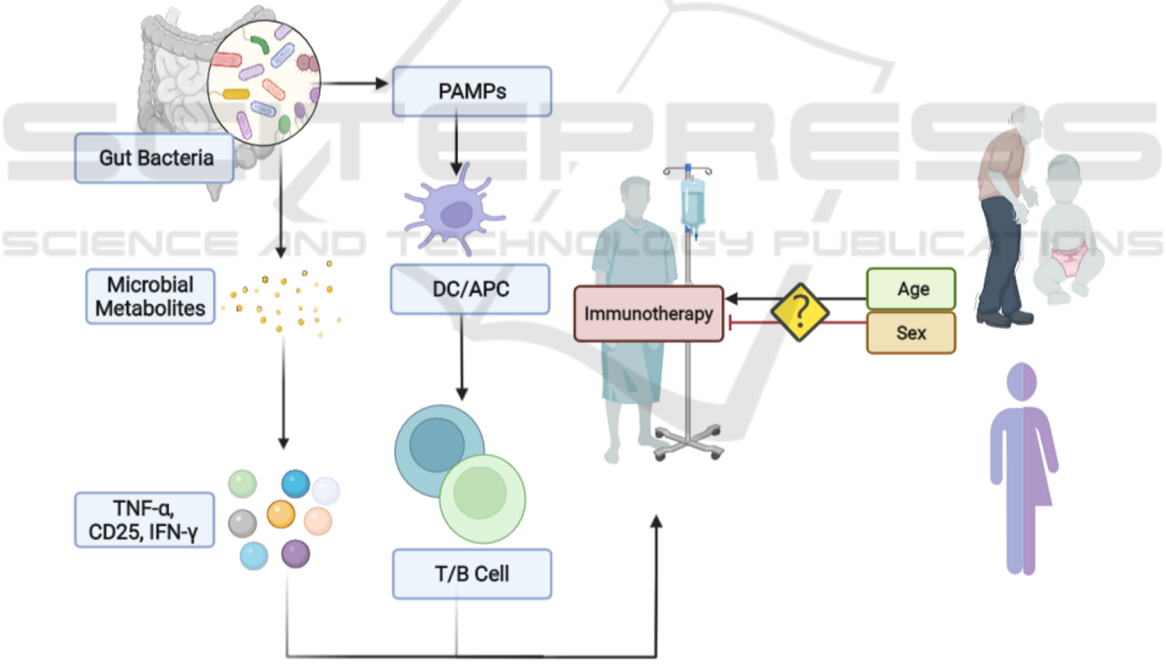

Figure 2: Host-related mechanism of resistance to cancer immunotherapy.

The association between age or gender and effects on immunotherapy response is controversial. The gut microbiome can activate PAMPs, which in turn recruits APCs to prime T and B cells. The composition of the gut microbiome is vital in influencing immunotherapy response. Gut microbiota has also been reported to up-regulate the production of TNF-α, CD25 and IFN-γ, which can enhance the effect of cancer immunotherapy.

5 DISCUSSION AND CONCLUSION

In this review, we have identified multiple mechanisms of immunotherapy resistance and potential areas for future research. Resistance to immunotherapy emerges from a complex list of factors which are tumor-cell intrinsic, extrinsic (Figure 3) or host-related. Research into patient stratification for immunotherapy and identifying resistance biomarkers are both essential in ensuring better treatment responses. With the emergence of various immunotherapy resistances, combination treatments with other targeted therapies have gradually entered the clinical stage. The main aim of this combination treatment is to use targeted therapies to block immunotherapy resistance mechanisms such as tumor intrinsic and extrinsic pathways mentioned in this review. The combination of CTLA-4 and PD-1 blockers has achieved great success in the clinic, lessening the resistance to the monotherapy in multiple types of cancer (Rotte, 2019). Similarly, indoximod was added to the treatment of pembrolizumab to overcome the resistance from the up-regulated expression of IDO (Zakharia et al., 2021). Combination of DNA hypomethylating agent (DHA) guadecitabine with anti-CTLA-4 antibody ipilimumab resulted in increased CD8+ infiltration and prevented resistance induced from HLA class I downregulation (Di Giacomo et al., 2019). Likewise, the pan-PI3K inhibitor copanlisib enhanced the effect of the monotherapy of immune checkpoint inhibitors (Yan et al., 2021). Identifying combination treatments that can improve the primary immunotherapy response and block immunotherapy resistance mechanisms is an important strategy needed to achieve better treatment results. Table 1 lists clinical trials of current combination therapy programs.

Table 1: List of combination therapy against the resistance to cancer immunotherapy.

Resistance Mechanism		Clinical Trial ID	Cancer Type	Cancer Characterization	Combination Therapy Agents	Targets (respectively)	Phase
Neoantigen	Lack of neoantigen	NCT03827044	Colon cancer	Stage III	5-FU + Avelumab	Chemotherapy and PD-L1	Phase 3
		NCT04397003	Small cell lung cancer	Extensive stage	Neoantigen DNA vaccine + Durvalumab	Neoantigen and PD-L1	Phase 2
		NCT03867175	Lung cancer	Metastatic or stage IV	Stereotactic Body Radiation + Pembrolizumab	Radiation therapy and PD-1	Phase 3
Alteration of cell intrinsic signaling pathway	PI3K/AKT signaling pathway	NCT03257722	Non-small cell lung cancer	Metastasic or Recurrent	Idelalisib + Pembrolizumab	PI3K-δ and PD-1	Phase 1b/2
		NCT03502733	Solid tumor or lymphoma	Metastatic or Recurrent or Unresectable or stage III/ IV	Copanlisib + Ipilimumab + Nivolumab	PI3K and CTLA4 and PD-1	Phase 1b
		NCT03190174	Sarcoma and certain cancers	Advanced	Nab-Rapamycin + Nivolumab	mTOR and PD-1	Phase 1/2
	ERK/MAPK signaling pathway	NCT01754376	Melanoma	Mutant in the BRAF gene	Vemurafenib + Aldesleukin(IL-2)	BRAF and T cells/NK cells	Phase 2
		NCT04163237	Liver cancer	Advanced	Sorafenib + PD-1	ERK/MAPK signaling pathway + VEGFR and PD-L1	Phase 3
		NCT03363867	Ovarian & Fallopian tube cancer & Peritoneal carcinoma	Recurrent	Cobimetinib + Bevacizumab + Atezolizumab	MEK and VEGF and PD-L1	Phase 2
	VEGF-related signaling pathway	NCT04715633	Colorectal cancer	Microsatellite instability high	Apatinib + Camrelizumab	VEGFR2 and PD-1	Phase 2
		NCT03517449	Endometrial cancer	Advanced	Lenvatinib + Pembrolizumab	VEGFR and PD-1	Phase 3
		NCT04356729	Melanoma	Stage III/ IV or unresectable	Bevacizumab + Atezolizumab	VEGF and PD-L1	Phase 2
		NCT01950390	Melanoma	Stage III/ IV or unresectable	Bevacizumab + Ipilimumab	VEGF and CTLA4	Phase 2
	HER-related signaling pathway	NCT04740918	Breast Cancer	Metastasic & HER-2+ & PD-L1+	Trastuzumab + Atezolizumab	HER-2 and PD-L1	Phase 3
		NCT03082534	Head & Neck Squamous Cell Carcinoma	Metastasic or Recurrent	Cetuximab + Pembrolizumab	EGFR and PD-1	Phase 2
Epigenetic regulation	Alteration of epigenetic regulation	NCT03765229	Melanoma	-	Entinostat + Pembrolizumab	HDAC and PD-1	Phase 2
		NCT02608437	Melanoma	Metastasic	SGI-110 + Ipilimumab	DNMT and CTLA-4	Phase 1

Tumor microenvironment	TAMs and MDSCs	NCT02452424	Melanoma and other solid tumors	Advanced	PLX3397 + Pembrolizumab	CSF1R and PD-1	Phase 1/2
		NCT02880371	Solid tumors	Advanced	ARRY-382 + Pembrolizumab	CSF1R and PD-1	Phase 1b/2
	Multiple Inhibitory Regulators	NCT03084471	Solid tumors	Advanced	Durvalumab + Tremelimumab	PD-L1 and CTLA4	Phase 3
		NCT03680508	Liver cancer	Primary or Advanced or Unresectable adult primary	Cobolimab + Dostarlimab	TIM-3 and PD-1	Phase 2
		NCT04370704	Melanoma	Advanced	INCAGN02385 + INCAGN02390 + INCMGA00012	LAG-3 and TIM-3 and PD-1	Phase 1/2
	Lack of T/NK Cells	NCT01629758	Solid tumors	-	Denenicokin(IL-21) + Nivolumab	T/NK cells and PD-1	Phase 1
		NCT02989714	Renal Cell Carcinoma	Metastasic	IL-2 + Nivolumab	T/NK cells and PD-1	Phase 1/2
	IDO	NCT02752074	Melanoma	Unresectable or metastatic	Epacadostat + Pembrolizumab	IDO and PD-1	Phase 3
Host-related	Host Microbiome	NCT04924374	Lung Cancer	Advanced	Microbiota capsule + Pembrolizumab/Nivolizumab/Atezolizumab	Gut microbiome and PD-1	Not Applicable
		NCT03341143	Melanoma	-	Fecal Microbiota Transplant + Pembrolizumab	Gut microbiome and PD-1	Phase 2

Immunotherapy treatment has been linked to producing a durable anti-tumor response and using combination therapy to prevent resistance mechanisms can enhance this. Currently, new strategies are being used to recruit patients to immunotherapy trials, such as measuring their tumor-infiltrating T cell counts, PD-L1 expression and MSI status (Hegde & Chen, 2020). However, current clinical practices still lack prediction biomarkers for immunotherapy resistance. Research into better companion diagnostic tools that can offer personalized immunotherapy regimes or combinations can provide a long-lasting response for patients.

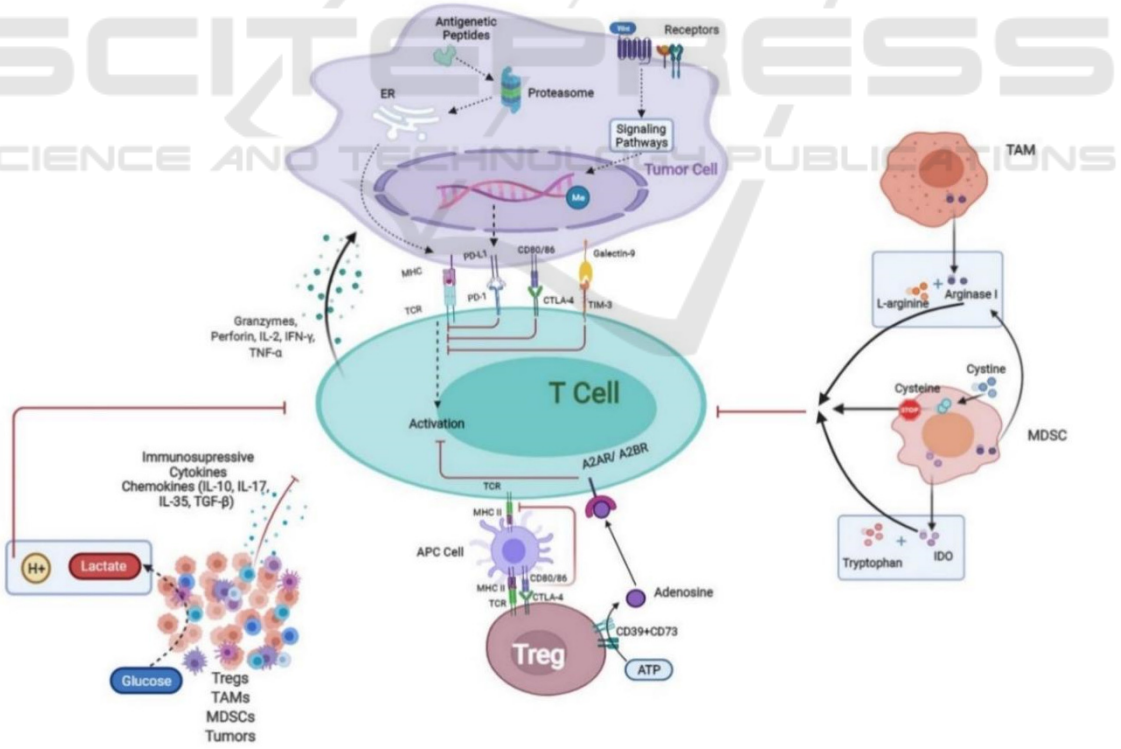

Figure 3: Tumor cell-intrinsic and TME-related mechanisms of resistance to cancer immunotherapy.

Tumor cell-intrinsic mechanism includes resistance via aberrant neoantigen presentation/processing, over activation of tumor-cell-intrinsic signaling pathway and epigenetic regulation. TME-related resistance mechanisms include **1)** increased infiltration of immunosuppressive cells, **2)** secretion of cytokines and chemokines, **3)** metabolism of glucose, amino acids and adenosine, and **4)** expression of multiple inhibitory regulators, resulting in dysfunction of the immune system.

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