Review Article

Immunotherapy Resistance in Non-Small Cell Lung Cancer: A Rubik's Cube to Assemble

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ABSTRACT

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer and is usually not diagnosed until an advanced-stage disease is present. Chemotherapy is the recommended treatment; however, it is known that chemotherapy alone has a low cure rate, harmful side effects, and a lack of sensitivity. Therefore, alternatives to improve the patient's experience and outcomes with immunotherapy are being used as first-line treatment in patients with NSCLC. Patients may develop primary or acquired resistance against immunotherapy, and the mechanisms of resistance are not yet fully understood. Currently, several new approaches are being developed to overcome immunotherapy resistance in NSCLC. Herein, we briefly discuss pathways driving resistance to immunotherapy and new alternatives that are being developed to overcome resistance.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer and accounts for 75–80% of such cases.[1] Clinical outcomes for NSCLC are related to the stage at the moment of diagnosis. Usually, it is not diagnosed until an advanced-stage disease is present, in which chemotherapy is the recommended treatment.[1] It is known that chemotherapy alone has a low cure rate, harmful side effects, and a lack of sensitivity. Therefore, alternatives to improve patient's experience and outcomes like immunotherapy (IO) are being used as first-line treatment in patients with NSCLC.[1–3]

IO targets the host's immune system, thereby prompting immune cells to recognize the tumor and later eliminate the already recognized tumor cells.[3] IO is revolutionizing treatment in NSCLC, remarkably acting in immune checkpoint inhibitors (ICI), like programmed death protein 1 (PD-1), by blocking cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and PD protein ligand 1 (PD-L1).[3,4]

An overall survival (OS) of 5 years is an expected long-term response in most advanced-stage patients treated with IO.[4] However, most patients develop primary or acquired resistance against IO.[3,4] Primary resistance, also known as intrinsic resistance, is when the tumor does not respond to IO; in NSCLC, only 15–20% achieve

partial or complete response.[3,5] Acquired resistance in NSCLC is when the tumor initially responds to IO, but after a median progression-free survival of approximately 4–10 months, the tumor stops responding.[3,5] Mechanisms of resistance are not yet fully understood. Currently, a lot of new approaches are being developed to overcome IO resistance in NSCLC. Herein, we discuss briefly pathways driving resistance to IO and new alternatives that are being developed to overcome IO resistance.

MECHANISMS OF RESISTANCE

Tumor Cell Intrinsic Mechanisms

The first of the genomic features that develop resistance against IO is the low tumor mutation burden (TMB). The TMB represents the total number of nonsynonymous mutations per DNA megabase. The nonsynonymous mutations generate neoantigens that lead to cytotoxic response against tumors. Therefore, a low TMB leads to an inadequate response to IO and to an inferior progression-free survival (PFS) in patients with NSCLC.[3]

The second of the genomic features is the increased neoantigen intratumor heterogeneity. The increase elevates the likelihood of selecting subclones with low immunogenicity. It is also reported that loss and defective neoantigen presentation could lead to resistance.[3]

The third of the genomic features that develop resistance is DNA repair, replication, and gene alterations. These changes cause genetic instability and lead to low TMB and the subsequent IO resistance in patients with NSCLC.[3]

The fourth of the genomic features are aberrations in oncogenes and tumor suppressor genes. Those genes regulate immune response by controlling cell composition and cytokine profile, making tumor cells resistant.[3]

The last and fifth genomic feature is the interferon-gamma signaling mutation because it leads to an upregulation of tumor growth and apoptosis inhibition.[3] Some evidence suggests that epigenetic modification may contribute to IO resistance, because of its antitumor immunity activity. In addition, the stability of chromatin remodeling complexes within tumor cells and transcriptomic signatures can also contribute to IO resistance by multiple mechanisms.[3]

Tumor Cell Extrinsic Mechanisms

Some T cell–related factors involved in the tumor-cancer immune cycle can lead to resistance against IO. Impaired T-cell priming and infiltration may disturb proliferation and diversification of T cells, contributing to IO resistance.[3] In addition, tumor-specific CD8+ T cells execute anticancer activities; some studies showed low CD8+ T cells correlated with poor efficacy and OS in patients with NSCLC treated with IO. It is also known that presence of tumor-infiltrating lymphocytes (TIL) correlates with proinflammatory cytokines, so the absence of TIL associates to resistance due to the absence of immune stimulation.[3] Besides, the responsivity of T-cell receptors by TILs plays a crucial role in antigen presentation cells, so a low baseline clonal T-cell arsenal is linked to IO resistance. Finally, it is also known that T-cell exhaustion is another factor involved in the primary and acquired resistance to IO.[3]

It is also reported that, upregulation of immune checkpoint receptors during IO cause activation of diverse cellular signals that are linked to IO adaptive resistance in NSCLC.[3] Another significant factor that relates to IO resistance is the tumor microenvironment (TME). The TME is compounded by immune and stromal cells, cytokines, extracellular matrix, and vasculature; all of that contribute to the inhibition or stimulation to immune responses. It also has been reported that increased immunosuppressive cells, elevated immunosuppressive cytokines, and the presence of additional immunoregulative molecules lead to IO resistance in patients with NSCLC.[3]

Host-Related Mechanisms

Sex is reported as a factor that may influence resistance against IO. Some results showed that IO is more efficient in males than in females. It is also known that older age is associated with restricted immune function, which could lead to the thought that aging could be associated with resistance against IO. However, some studies reported that efficacy and safety are similar in young and old patients.[5]

Multiple studies have reported that less bacterial diversity in gut microbiome is associated with resistance against IO. Many studies reported improvement in IO therapy when responding patients' feces were transplanted into aseptic mice.[3,5] In addition, antibiotics exposure has been reported to be associated with inferior clinical outcomes during IO in NSCLC. Antibiotics exposure leads to less bacterial diversity on the gut microbiome, because of the unfavorable impact on gut's recolonization. Moreover, antibiotics exposure destroys gut homeostasis and has long-lasting adverse effects on the immune system.[3,5] Disproportionate corticosteroid use is also known to affect the efficacy of IO in NSCLC. Because of their anti-inflammatory and immunosuppressive effects, they induce an imbalance of immune cells in TME.[3] Diet also influences resistance against IO because it alters the gut microbiome, and some ingredients, like vitamins, may impact the immune status. Therefore, an appropriate diet can maintain the homeostatic equilibrium between the inflammatory cascade triggered and the anti-inflammatory pathway.[3]

Chronic inflammatory status and autoimmunity lead to imbalanced immune homeostasis, which is linked to IO resistance. Finally, a relationship between smoking and IO efficacy remains controversial. Smoking has been linked to IO resistance because of its poor impact on some immune modulators. However, it is also associated

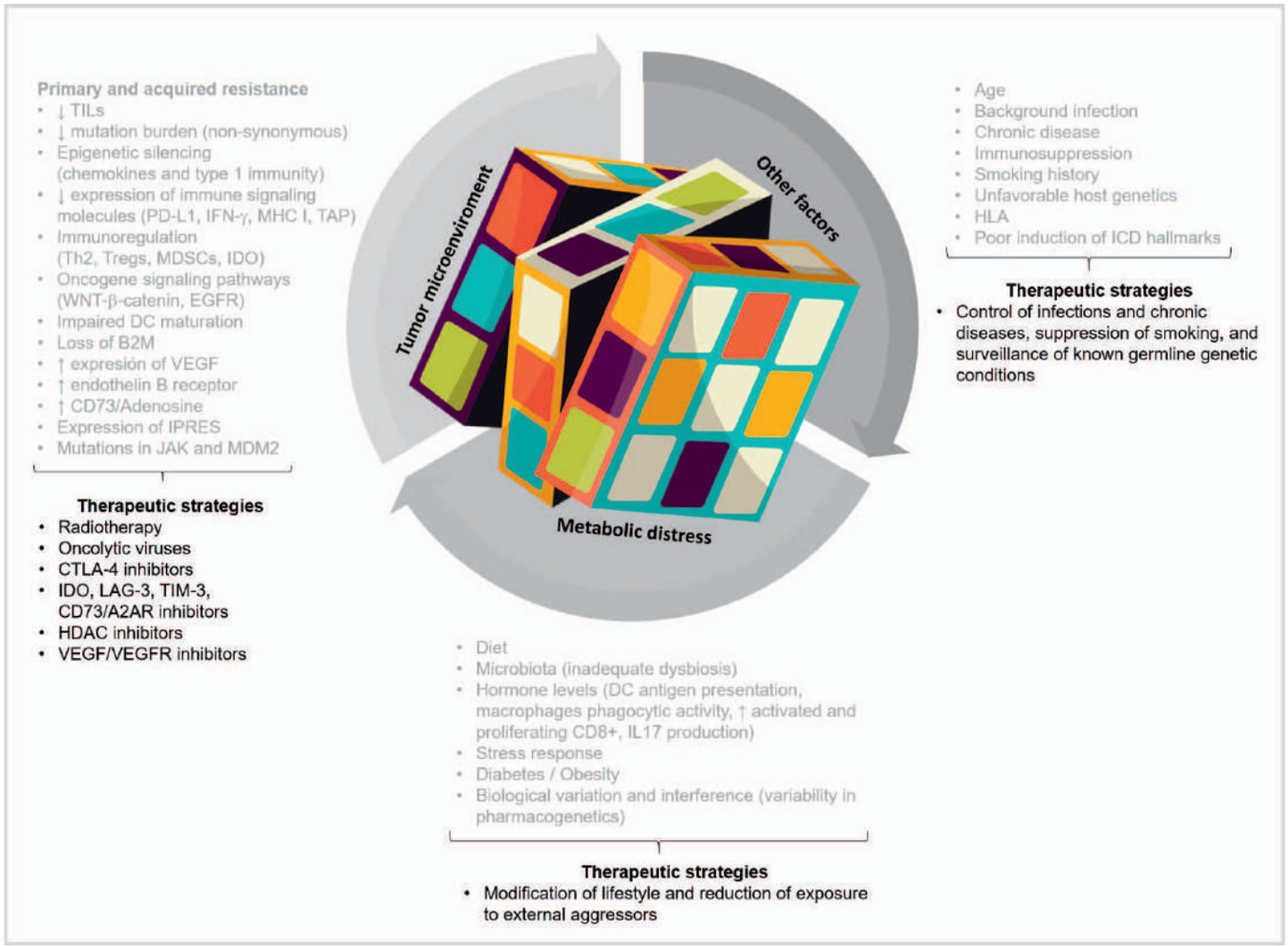

Figure 1. Many potential tumor-related, host-related, and environmental factors can explain the degree of heterogeneity within disease control seen with immunotherapy. These can be categorized into influences from the tumor microenvironment, endocrine and metabolic factors, environmental factors, and others, such as age and unfavorable host genetics. A2AR: A2A receptor; B2M: beta-2-microglobulin; DC: dendritic cells; HDAC: histone deacetylase; IDO: indoleamine 2,3-dioxygenase; IFN-g: interferon gamma; IPRES: innate anti–PD-1 resistance signature; JAK1/JAK2: janus kinases 1 and 2; LAG-3: lymphocyte activation gene 3; MHC I: major histocompatibility complex I; TAP: transporter associated with antigen processing; TILS: tumor infiltrating lymphocytes; IFN-g, interferon gamma; MHC I, major histocompatibility complex I; TAP, transporter associated with antigen processing; DC, dendritic cells; A2AR, A2A receptor; B2M, beta-2-microglobulin; HDAC, histone deacetylase; JAK1/JAK2, janus kinases 1 and 2; IDO, indoleamine 2,3-dioxygenase; IPRES, innate anti–PD-1 resistance signature; LAG-3, lymphocyte activation gene 3; TIM-3: T-cell immunoglobulin and mucin domain 3; Tregs: regulatory T cells; VEGF: vascular endothelial growth factor.

with high TMB, which enhances the tumor's immunogenicity and improves IO response.[3] Figure 1 shows major factors contributing to resistance related to IO.

New Alternatives to Overcome Immunotherapy Resistance

A lot of novel alternatives have been developed to overcome IO resistance in patients with NSCLC. The combination of diverse immunotherapeutic agents or with traditional therapies is one of the new approaches explored.

Alternatives to Overcome Tumor Cell Intrinsic Resistance

The target of the first alternative are oncogenic genes. A combination of IO with other treatments, aim to block some signaling pathways to avoid T-cell exhaustion and apoptosis. We are achieving this by activating immune stimulation and promoting proinflammatory cytokines and T-cell cytotoxicity.[3,5] Another alternative is to enhance tumor immunogenicity. Some studies reported that the combination of IO and chemotherapy has a positive immunologic effect. This effect occurs because chemotherapy overcomes IO resistance by upregulating tumor antigen presentation and increasing tumor cell apoptosis by regulating the composition and function of the immune response. [3,6] The combination of chemotherapy, radiotherapy, and IO also leads to tumor regression by increasing neoantigen exposure secondary to cancer cell apoptosis and inflamed TME. It also causes an upregulation of proinflammatory cytokines, leading to elevated TILs.[3,4] Finally, achieving epigenetic modu-

lation with DNA methyltransferase inhibitors and histone deacetylase inhibitors is also an alternative for overcoming IO resistance.[3]

Alternatives to Overcome Tumor Cell Extrinsic Resistance

First, the use of antibodies that target immune checkpoints, causing blockade of alternate coinhibitory receptors, agonists costimulation, and T-cell expansion increase, can overcome resistance against IO.[3,4] Second, reshaping immunosuppressive TME by blocking and suppressing some receptors and targeting suppressive factors of the TME overcome IO resistance. These two procedures reduce tumor invasion, improve TME status, and facilitate tumor penetration, leading T cells to cause reversion of immunosuppressive TME.[3,4] Finally, promotion of T-cell priming by activating inflammatory reactions via interferon-α cascade upon recognition of foreign DNA, increases TILs and T-cell cytotoxicity. That procedure, combined with monoclonal antibodies, immune regulators, or targeting dual immunomodulators has been shown to reduce resistance against IO.[3,4,7]

Alternatives to Overcome Host-Related Resistance

The combination of IO with diet, probiotics, and fecal microbiota transplantation are alternatives to modulate gut microbiota.[3,4]

CONCLUSION

IO could be the answer for patients with NSCLC, but many IO resistance mechanisms have been described, and more continue to be uncovered. It is necessary to develop alternatives that decrease risk of resistance and prolong IO therapeutic benefits.

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