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Review Article

Gut Microbiome and Mechanisms of Primary and Acquired Resistance To PD-1/PD-L1 Blockade

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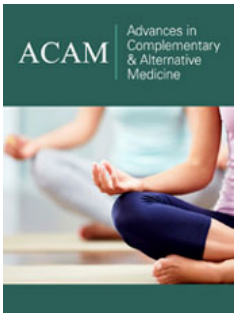

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Abstract

PD-1/PD-L1 blockade is a promising immunotherapy, which provides a new method for the treatment of a variety of tumors and has significant clinical efficacy. However, most patients are not initially sensitive to these therapies, known as primary resistance. Unfortunately, some patients develop acquired resistance even after an initial response to PD-1/PD-L1 blockade. In fact, the mechanisms of primary and acquired resistance are not fully and clearly understood. Recently, the role of gut microbiome has also become a hot topic of research. From the above aspects, this article will discuss the related mechanisms and new strategies to improve the curative effect.

Keywords: Immune checkpoint blockade therapy; Immunotherapy resistance; Microbiome

Introduction

Immunotherapy has certainly opened up a promising new field of research in cancer treatment. A variety of malignant tumors, such as metastatic melanoma, non-small-cell lung cancer (NSCLC), head and neck squamous cell cancer, Hodgkin's lymphoma, renal cell carcinoma, urothelial carcinoma, Merkel cell carcinoma, gastric carcinoma, and hepatocellular carcinomas [1-15]. Frustratingly, the efficacy of monotherapy for PD-1/PD-L1 blocking is generally less than 40% in most malignancies [5,16]. Approximately 60% of patients with melanoma, the most sensitive type of tumor to immunotherapy, also show primary resistance to PD-1/PD-L1 blocking therapy [16]. The initial effect of treatment would wear off over time, resulting in continued deterioration or recurrence [17].

Microbial imbalance plays a significant role in cancer as well. Certain bacteria and their metabolites contribute greatly to the restoration of natural beneficial microbiome [18]. In brief, this review will focus on the complex and dynamic mechanisms responsible for resistance to immunotherapy via PD-1/PD-L1 blockade and the gut microbiome.

Resistance Mechanisms

Lack of tumor immunogenicity

Expression and presentation of antigens and neoantigens are the core of T cells' ability to recognize tumors and participate in TCR. T cells lack the capacity to recognize tumors due to absence of tumor antigens, which directly gives rise to the inability of host CD8+ T cells to localize to tumors [19]. Therefore, anti-PD-1 /PD-L1 therapy is more effective in tumors with high mutation load and increased neoantigen expression, including melanoma, NSCLC, and microsatellite unstable tumors [5,20-22]. In contrast, tumors with fewer somatic mutations, like pancreatic and prostate cancers, are generally less sensitive to PD-1/PD-L1 blocking [21,23].

In addition, Cancer cells would silence or alter the expression of antigen-presenting machinery, beta-2-microglobulin (β2M) or MHC molecules, thereby preventing antigen processing and presentation to the cell surface [24,25]. Excessive cell proliferation and DNA damage caused by chronic inflammation can induce CRP to increase the mutational burden of local tumors, reducing the resistance of tumors to PD-1 therapy [26].

Tumor microenvironment and T cell exclusion

A phenomenon called T cell exclusion may happen in metastatic melanoma, bladder transitional cell carcinoma etc., which is caused by primary mutational events within

the tumor. T cells tracking to the tumor microenvironment are inhibited without influencing antigen expression or presentation. Some abnormal cell signal transduction pathways, such as PI3K/AKT pathway, WNT/β -catenin pathway, mitogen activated protein kinase (MAPK) pathway and NF-κ B pathway, are essential to explain this phenomenon [27].

However, chronic infection and cancer expose CD8+ T cells to continuous antigenic stimulation, on which PD-1 expression gradually occurs. Stimulation of PD-1 can result in another state of T cell dysfunction, called T cell exhaustion. The depleted T cells possess poor effector function, suppressed receptor expression and abnormal transcriptional status. PD-1 blockade can reactivate these hypofunctional "exhausted" CD8+ T cells (TEX) and restore their function to fight tumors [28].

Tumeh et al. found that preexisting CD8+ T cells are the prerequisite for tumor regression after PD-1/PD-L1 blocking therapy in metastatic melanoma, suggesting that tumor-infiltrating lymphocytes are important components of the response to anti-PD-1 therapy [29]. In fact, in addition to tumor cells, there are many components in TME that may be related to primary or acquired drug resistance, including myeloid derived suppressor cells (MDSCs), Tregs, TAMs, IDO and so on. They are closely related to tumor cells, protecting tumor cells from detection and destruction through immune monitoring [30]. Apart from immune regulation factors, co-enrichment of a set of 26 transcriptomic markers (known as IPRES signatures) is also involved in primary resistance to PD-1/PD-L1 [17, 31].

Tumor cell resistance to interferon

CD8+ T cells that have identified and participated in appropriate tumor antigens can produce IFN-γ, thereby increasing MHC expression/antigen presentation, attracting more T cells into tumors, and directly inducing anti-proliferation and apoptosis of cancer cells [32]. The success of any T-cell-based immunotherapy such as PD-1/PD-L1 blockade is dependent on the response of interferon to tumors. Although mutations within interferon signaling elements have been described in the setting of primary resistance to treatment, chances are that these mutations occur after treatment has begun [27]. Besides reflecting the dynamic response of IFN-γ, PD-L1 expression can also be expressed constitutionally under certain circumstances. Patients diagnosed with NSCLC with EGFR mutations and ALK rearrangement are extremely insensitive to PD-1/PD-L1 inhibitors [33-35].

Gut microbiome

Microbial imbalance, such as reduced bacterial population and changes in their species composition, can contribute to tumorigenesis or immunotherapy failure. By promoting nutrient absorption, metabolism and immune development, gut microbes can promote tissue growth and differentiation, which increases the risk of cancer greatly [36]. Research found that mutated p53 drives tumor inhibition by disrupting the WNT pathway, through preventing TCF4 from binding to chromatin. Frustratingly, this inhibitory effect can be eliminated by gut microbiome completely [37]. However, on the other hand, gut microbiome is a beneficial potential regulator, which tightly connects intestinal cells, reduces intestinal permeability, and inhibits carcinogenicity to a certain extent [38]. Adoptive metastasis of tumor-specific T cells induces translocation of intestinal flora from the lumen to mesenteric lymph nodes in mice, demonstrating for the first time the positive effect of intestinal flora in cancer treatment [39]. Gut microbiome can reverse the resistance to immunity via increasing production of cytokines, enhancing the activation of DCs, decreasing peripherally derived Tregs, inducing the overexpression of chemokines and so on [38]. Shotgun metagenomes from the same sample revealed that patients with different responses differed in the abundance of pathways related to nucleoside and nucleotide biosynthesis, lipid biosynthesis, glucose metabolism, and fermentative short-chain fatty acids (SCFAs). The presence of gut bacteria capable of producing SCFA, like Eubacterium, Lactobacillus, and Streptococcus, significantly enhances patients' response to anti-PD-1/PD-L1 across different types of GI cancer [40]. Actually, the adjuvant role of gut microbiome in the immune checkpoint inhibitor treatment of advanced melanoma, including NSCLC, RCC, and urothelial carcinoma has attracted considerable attention [41,42]. In a mouse model, Daillere and colleagues identified that Enterococcus hirae and Barnesiella intestinihominis are key steps in the anti-tumor and immunomodulatory properties of cyclophosphamide [43,44]. Grifn et al. [18] suggested that oral administration of Enterococcal bacteria, including *E. hirae*, *E. Durans*, and *E. Mundtii*, is an effective method of anti-PD-L1 immunotherapy. Wang et al. [45] believed that *A. muciniphila* could regulate intestinal homeostasis and reshape the immune environment. An experiment by Zheng et al. [46] showed that fecal samples from patients who responded to immunotherapy were more likely to be found with high abundance and a variety of bacterial genes. Take a typical example is that almost all fecal samples from patients who responded to treatment with camrelizumab were able to find approximately 20 species, such as *Akkermansia Muciniphila* and Ruminococcaceae SPP.

In fact, the pattern of interaction between gut microbes and the host immune system still needs to be further identified. Three possible ideas have been proposed:

(1) via T cell responses induced by microbial antigens,

(2) via the involvement of pattern recognition receptors, and

(3) via small molecules produced by microbial metabolism [47]

Meanwhile, probiotics, as a kind of microbe promoting human health, can inhibit the proliferation of tumor cells through regulating gut microbiome [48] and immune regulation [49,50]. The remarkably decreased expression of the inflammatory cytokine IL-17 in tumors was closely affiliated with the inhibition of Th17 cell population and Th17 cell infiltration in intestinal and peripheral circulation. Probiotics supplementation also helped up-regulate the expression of the anti-inflammatory cytokines IL-10, IL-13, and IL-27 [51].

Conclusion

Although PD-1/PD-L1 blocking immunotherapy has shown great promise in the treatment of various advanced cancers, there are still many difficulties, and there is still a long way to go to improve the efficacy of PD-1/PD-L1 blocking therapy comprehensively and individually. Given the complexity of the interaction between cancer and the immune system, multi-drug combination therapy may be a better option than single-drug therapy. For example, the coadministration of PD-1/PD-L1 blockade with tumor necrosis factor inhibitors [52,53], metformin [54], anti-VEGF drugs [55], or other immune checkpoint inhibitors (such as CXCR4[56]) has been verified to amplify anti-tumor efficacy and reduce toxicity. With the further study of gut microbiome and immunotherapy biomarkers, researchers will open more new research fields and directions in tumor immunotherapy. In all, with mechanisms responsible for resistance continuing to be characterized, therapies can be personalized and change in real time according to patients' responses and condition, effectively overcoming relapse. More comprehensive and personalized treatment strategies are bound to contribute to more and more patients.

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