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Challenges In Cancer Immunotherapy

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Abstract

The concept of deploying the immune system to treat neoplastic diseases emerged in the nineteenth century. It made significant progress in the twentieth century with the advent of new technology. Various immunotherapy treatments exist, including cancer vaccines, monoclonal antibodies, cytokines, adjuvants, tumor-infecting viruses, and adoptive immunotherapy. The different types and approaches of immunotherapy have revolutionized the field of oncology by increasing the survival of patients with fatal cancers. Despite these advances, there are still many obstacles in immunotherapy. This review will discuss the challenges in immunotherapy, including the need for more predictive biomarkers, tumor heterogeneity, and resistance to drugs.

Keywords: Programmed death ligand 1 [PDL-1]; Immune Checkpoint Blockers; Chimeric antigen receptors (CARs); Monoclonal antibodies; Gut microbiota

Biomarker identification

Around 140 genes have been identified that, when altered, can drive tumorigenesis. These "driver" genes can be categorized into 12 pathways that regulate three major cellular pathways and are processed, such as genomic maintenance, cell survival, and cell fate [1]. A better understanding of these pathways is required to further immunotherapy research. One of the molecules well-studied in the cell survival pathway is the programmed death ligand 1 [PDL-1] in tumor cells. One way to prevent programmed death-1 (PD-1) in T-Cells, from interacting with PDL-1 in tumor cells is by using Immune Checkpoint Blockers [ICB]. In a study dedicated to checking for cancer checkpoint inhibitors, it was found that ICB treatment only worked for about 15% to 25% of patients due to the presence of multiple checkpoint pathways and their role in anti-cancer immune responses [6-8]. Targeting such receptors in cancer could be difficult due to the development of novel mutations. These mutations could be responsible for changes in biomarker expression, making it challenging for scientists to develop treatments. Another impediment on the road to successful ICB treatment is that the functionality of ICB treatments is dependent on the number of mutations in tumor cells [3-6]. Such treatments work with cell types with higher mutations since they stimulate CD8+ and CD4+ T-Cells. Tumors with low mutations have fewer receptors, making it harder for the immune system to identify them. Scientists need to understand such intricate mutations to develop specific ICB therapies. Sequencers like the Classic Sanger Genomic Sequence, which lacks sufficient sensitivity, can't detect mutations in the genome. This sequencer can only test for multiple genomic mutations or small insertions and deletions, and the cost for such sequencing is very costly [8]. In-depth sequencing is needed to identify multiple mutations. One such effective NGS method is customized gene panels. These customized gene panels have been used in many clinical trials and effectively provide patient-specific treatments. They are primarily utilized in academic centers that specialize in genetic research. However, such an advanced tool is not widely available, preventing many people from receiving personalized treatment [8]. A significant challenge with NGS is the cost. This applies to any NGS since data interpretation often involves a team of experts.

However, such tools are necessary for patients with an advanced cancer prognosis. Those patients suffering from an advanced stage of cancer especially require NGS therapies

specializing in clinical therapy. Some treatments, like monoclonal antibodies, target one biomarker or a single cancer pathway. A successful example is Herceptin (trastuzumab), a monoclonal antibody that targets the epidermal growth factor receptor in breast cancer [15]. However, Herceptin has also been extended to patients with gastric cancers with Her^2 amplification. Only about 20% of gastric cancer patients have Her^2 amplification; out of that, a mere 40-50% showed a positive outcome [8]. However, targeting a single pathway/ protein could be a "reductionist" approach, given the complexity of tumor pathways. Treatment strategies that target a combination of one or more pathways or mutations could be one way to get around this problem.

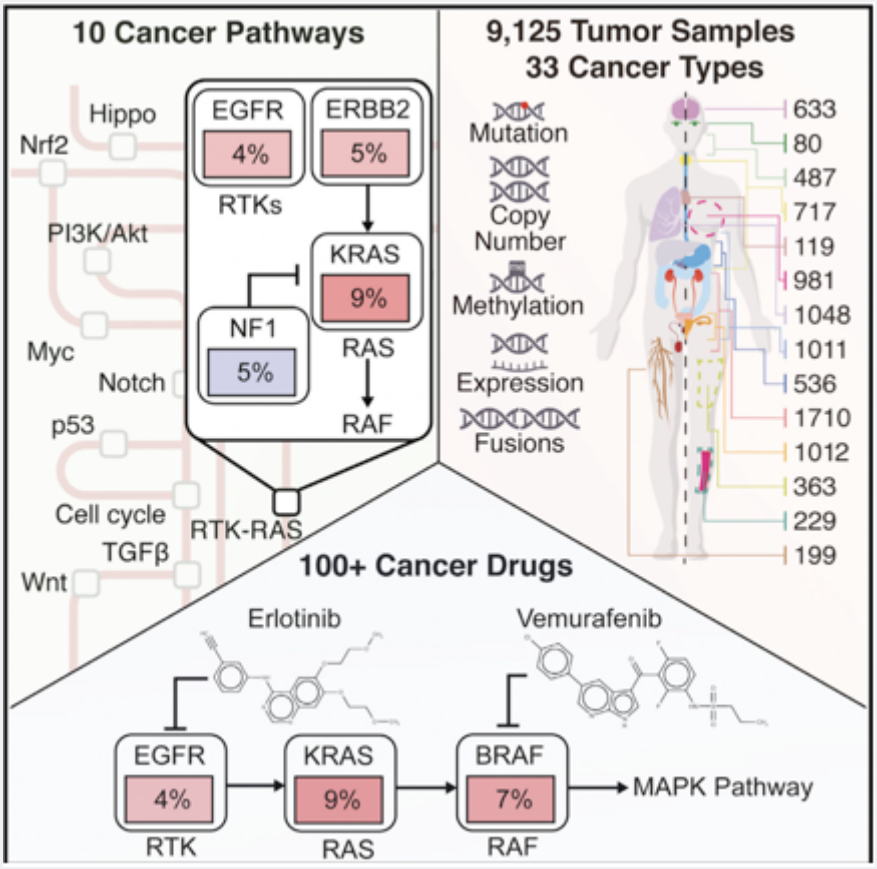

Figure 1: 9,125 tumor samples were taken from 33 Cancer types and 10 specific cancers using Next Generation Sequences such as The Cancer Genome Atlas (TCGA) [10]. Specific pathways were found to be expected in all tumors (figure recreated from reference [10]).

Resistance and Tumor Heterogeneity

Resistance to ICB pembrolizumab develops due to mutations in genes JAK1, JAK2, and B2M. Mutation in these genes decreases the expression of genes required for T-cell recognition. This resistance could cause secondary genomic mutations, cancer pathways reactivation, and alternative signaling pathways activation [12]. While genomic mutation has been characterized to some extent, non-genomic alterations like epigenetic modifications and transcriptional changes have not been studied well. Such alterations can also cause resistance to therapies [8]. Such heterogeneity does not allow for the development of specific targets in immunotherapy.

Role of the gut microbiota

Recent research has shown that the microbiota plays a role in cancer progression either through indirect or direct interaction with tumor cells. Close observation of the microbiota is pivotal for advancing immunotherapy, specifically checkpoint inhibitors. Interaction of different cancer pathways in the microbiota could advance research, allowing for future breakthroughs for targeting resistance to Immune checkpoint inhibitors [12-14]. The gut microbiome has been shown to significantly impact the response to checkpoint inhibitors (CPIs) in both animal models and humans. Several studies have demonstrated that individuals with certain microbial profiles have higher progression-free survival and overall survival treated with CPIs. For example, meta-

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static melanoma patients with baseline gut microbiota enriched with *Faecalibacterium* and other Firmicutes had higher progression-free survival (PFS) and overall survival (OS) when treated with ipilimumab [16]. In addition, the abundance of *Akkermansia muciniphila* in stool at the time of diagnosis was associated with better response to CPIs for renal cell carcinoma patients [17], and Lactobacilli and Clostridia were linked to prolonged time to treatment failure in non-small cell lung cancer patients treated with CPIs [18]. On the other hand, some microbial profiles have been associated with resistance to CPIs, such as gut microbiota profiles rich in *Ruminococcus obeum* and *Roseburia intestinalis* [19]. While the effects of microbial profiles on CPI responses have been observed in different studies, there is still no consistently identified bacterial taxon associated with the response to CPIs [20-16]. This The microbial world is pivotal for the understanding of the functionality of Cancer Checkpoint Blocker (CIB). Altering the microbial profile with various of therapies, such as Fecal microbial transplantation (FMT), probiotics, and lifestyle changes, m a crucialm step in overcoming CPI resistance in many cancer patient with poor outcomes after immunotherapy.

Conclusion

A proven and vitally important method for treating cancer patients is cancer immunotherapy. Given the extensive clinical inquiry and research efforts devoted to expanding both endogenous and synthetic immunotherapy techniques, there is a need to concentrate on key issues and identify impediments to the development of clinical practice and fundamental knowledge. Here, we outline the top few obstacles to cancer immunotherapy, which range from a lack of trust in translating pre-clinical results to the need to determine the best immunotherapy combinations for any individual patient. With all the challenges of immunotherapy, it is not easy to fight cancer, given the number of pathways and biomarkers (due to the heterogeneous population.) The treatment's efficacy depends on the stage and severity of cancer, as mutations and genetic diversity are the problems that force researchers to develop new therapeutic drugs to fight off further resistance. Specific tools are needed, which are not widely available, limiting specific therapy. Furthermore, CSC plasticity adds to this one of the major challenges for Immunotherapy. Subclonal cancer cells and branched evolutions can adapt fast to rising mutations. Given that we could target a limited number of mutations, more research is required to advance in this field. It will take the combined efforts of fundamental scientists and medical professionals to overcome these obstacles, as well as the concentration of resources, to hasten the knowledge of the intricate connections between cancer and the immune system and create better cancer treatment alternatives.

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