Editorial

Chunhong Zheng and Zemin Zhang*

New era of cancer immunology driven by big data

https://doi.org/10.1515/mr-2023-0070

Cancer immunology has witnessed remarkable development over the past century. In the early 20th century, William Coley embarked on pioneering efforts to activate the immune system against cancer using heat-killed *Streptococcus pyogenes* and *Serratia marcescens* [1]. These attempts yielded varying clinical outcomes, some of which were notably successful, providing early evidence of the immune system's potential in combating cancer. Moving into the mid-20th century, Dr. Lewis Thomas and Dr. Macfarlane Burnet introduced the concept "immune surveillance" [2]. This theory proposed that the immune system constantly monitors the body, identifying and eliminating emerging cancer cells to prevent them from developing into full-fledged tumors. This concept laid the foundation for future research in cancer immunology. Simultaneously, the concept of immune evasion emerged, emphasizing how cancer cells can elude immune detection and destruction, enabling them to proliferate and spread within the body. Thus, understanding and overcoming these mechanisms of immune escape became a pivotal focus of cancer immunotherapy.

Over the ensuing decades, various strategies were developed to counteract cancer cells' evasion tactics. Notably, immune checkpoint blockade therapy gained prominence, rooted in the discovery of immune checkpoints in the 1990s by James Allison and his team. They successfully identified the first immune checkpoint inhibitor molecule, CTLA-4, capable of regulating T cell activity and preventing excessive immune responses [3]. Concurrently, the PD-1 and PD-L1 pathway came into focus, leading to the development of drugs like pembrolizumab and nivolumab [4]. These drugs demonstrated remarkable efficacy against various cancer types, including melanoma and lung cancer. In recognition of their pioneering work on immune checkpoints and the development of checkpoint inhibitor therapies, James Allison and Tasuku Honjo were awarded the Nobel Prize in Physiology or Medicine in 2018. Moreover, ongoing exploration of other checkpoint proteins and genes aims to enhance the effectiveness of immunotherapies. However, the pool of potential novel targets for immune checkpoint inhibitors remains limited, primarily originating from established traditional immune-related signaling pathways like TIGIT, TIM-3, and LAG-3. Consequently, identifying and developing additional novel immune checkpoint targets with therapeutic potential remains both a critical and challenging task.

Fortunately, the emergence of next-generation sequencing (NGS) technology has brought about a revolution in the field of cancer immunology. Over the past decade, NGS technology has generated an enormous volume of sequencing data, with the aim of enabling comprehensive profiling of tumor genomes and transcriptomes [5]. This has allowed for the characterization of tumor genetic and transcriptomic signatures, ultimately leading to the discovery of predictive biomarkers for different immunotherapy response in clinical trials. Notably, some studies have delved into the genomic profiles of patients undergoing immune checkpoint blockade therapies, employing bulk exome sequencing methods. Through these investigations, a significant revelation emerged: a high tumor mutational burden (TMB) and microsatellite instability (MSI) were identified as markers associated with a greater likelihood of responding positively to immune checkpoint inhibitors [6]. In recognition of their significance, TMB and MSI were incorporated into clinical guidelines by the U.S. Food and Drug Administration (FDA) in 2018. These biomarkers empower clinicians to customize immunotherapy treatments for individual patients, thus maximizing therapeutic benefits while minimizing potential side effects.

Concurrently, the substantial influence of "big-data" derived from single cell sequencing has also shaped modern cancer immunotherapy. In 2009, Tang et al. published one of the earliest studies showcasing the sequencing of mRNA from individual mouse embryonic stem cells, marking a significant leap towards high-throughput single-cell RNA sequencing (scRNA-seq) [7]. Following this breakthrough, various methods for scRNA-seq were developed, including the Switching Mechanism At the end of the 5′-end of the RNA Transcript sequencing (SMART-seq) method [8], microfluidic

***Corresponding author: Zemin Zhang**, BIOPIC, Beijing Advanced Innovation Center for Genomics, School of Life Sciences, Peking-Tsinghua Center for Life Sciences, Peking University, Yiheyuan Road #5, Beijing 100871, China, E-mail: Zemin@pku.edu.cn

Chunhong Zheng, Peking University International Cancer Institute, Peking University Cancer Hospital and Institute, Health Science Center, Peking University, Beijing, China

chip-based platforms such as Fluidigm C1 [9], and droplet-based systems like 10× Genomics [10]. Initially, single-cell sequencing technology primarily found its applications within the field of cancer research, playing a pivotal role in enhancing our understanding of cellular heterogeneity and the diversity of tumor cells at the single-cell level [11]. However, the single-cell transcriptomic profiling of tumor infiltrating lymphocytes, which were considered the most crucial cell subset due to their capacity to target and eliminate tumor cells within the tumor microenvironment, remained largely unexplored.

Therefore, our team embarked on a pioneering endeavor by refocusing our efforts on the study of tumor-infiltrating T cells (TILs) through the utilization of single-cell sequencing technology. Our initial investigation involved a comprehensive analysis of individual T cells from six patients with hepatitis B virus (HBV) positive liver cancer. We employed a combined analysis of transcriptional profiles and T-cell receptor (TCR) sequences from over 5,000 single cell RNA-seq data [12]. This study provided intricate insights into the clonality and phenotypic characteristics of distinct T cell states, yielding a wealth of bioinformatics data. Notably, we identified unique gene signatures associated with exhausted CD8+ T cells and regulatory T cells (Tregs), such as Layilin (LAYN) and C-C Motif Chemokine Receptor 8 (CCR8), which were considered novel therapeutic targets for cancer immunotherapy. Consequently, our study is recognized as one of the pioneering efforts in characterizing the exhausted immune microenvironment in liver cancer at the single-cell resolution. Building upon this work, we leveraged state-of-the-art single-cell sequencing technology to explore the transcriptomic profiles of tumor infiltrating T cells across a range of cancer types, providing a holistic exploration of T cell behavior within the tumor microenvironment from a pan-cancer perspective [13]. In addition to T cells, other tumor infiltrating cell types, such as myeloid and NK cells, have made significant contributions to the field of cancer immunology. To delve deeper into this complexity, we harnessed high throughput single cell sequencing data, comprising 138,161 single cell RNA-seq datasets from 210 patients across 15 human cancer types for myeloid cells and 160,011 single cell RNA-seq datasets from 716 patients across 24 human cancer types for NK cells [14, 15]. These massive single-cell sequencing datasets offered a panoramic view of immune cell behavior within the tumor microenvironment, transcending the boundaries of individual cancer types. They provided invaluable insights into the complexity of antitumor immune responses, surpassing the capabilities of traditional cancer immunology research systems. This suggests promising future avenues for rational and targeted immunotherapies through in-depth bioinformatics analysis of these "big data".

Furthermore, the comprehensive meta-analysis of tumor infiltrating immune cells using single cell RNA-sequencing technology has enabled a high-resolution examination of individual cell responses to cancer immunotherapy. One of our studies delved into the intricate world of immune cell responses in the context of PD-L1 blockade therapy for triple-negative breast cancer [16]. This investigation unveiled critical immune cell populations associated with therapy response, providing crucial insights into optimization of immunotherapeutic approaches for cancer treatment.

In summary, the new era of cancer immunology, driven by the power of big data, represents a paradigm shift in our approach to understanding, treating, and ultimately defeating cancer. The capacity to process and analyze vast datasets has opened doors to previously unimaginable insights into the complex relationship between the immune system and cancer. As big data continues to fuel research and clinical applications, the future holds great promise for more effective, personalized, and targeted cancer immunotherapies. This offers renewed hope to patients and researchers alike in the battle against cancer.

Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: C.Z. drafted the manuscript; Z.Z. conceived the idea and contributed to the writing of the manuscript.
Competing interests: The authors state no conflict of interest.
Research funding: This work was supported by the National Natural Science Foundation of China (91942307).
Data availability: Not applicable.

References

1. McCarthy EF. The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas. Iowa Orthop J 2006;26:154–8.
2. Ribatti D. The concept of immune surveillance against tumors. The first theories. Oncotarget 2017;8:7175–80.
3. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. Science 1996;271:1734–6.
4. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. J Clin Invest 2015;125:3384–91.
5. Klijn C, Durinck S, Stawiski EW, Haverty PM, Jiang Z, Liu H, et al. A comprehensive transcriptional portrait of human cancer cell lines. Nat Biotechnol 2015;33:306–12.
6. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–20.

7. Tang F, Barbacioru C, Wang Y, Nordman E, Lee C, Xu N, et al. mRNA-Seq whole-transcriptome analysis of a single cell. Nat Methods 2009;6: 377–82.
8. Picelli S, Faridani OR, Björklund AK, Winberg G, Sagasser S, Sandberg R. Full-length RNA-seq from single cells using Smart-seq2. Nat Protoc 2014;9:171–81.
9. DeLaughter DM. The use of the Fluidigm C1 for RNA expression analyses of single cells. Curr Protoc Mol Biol 2018;122:e55.
10. Zheng GXY, Terry JM, Belgrader P, Ryvkin P, Bent ZW, Wilson R, et al. Massively parallel digital transcriptional profiling of single cells. Nat Commun 2017;8:14049.
11. Tirosh I, Izar B, Prakadan SM, Wadsworth MH, Treacy D, Trombetta JJ, et al. Dissecting the multicellular ecosystem of metastatic melanoma by single-cell RNA-seq. Science 2016;352:189–96.
12. Zheng C, Zheng L, Yoo JK, Guo H, Zhang Y, Guo X, et al. Landscape of infiltrating T cells in liver cancer revealed by single-cell sequencing. Cell 2017;169:1342–56.e16.
13. Zheng L, Qin S, Si W, Wang A, Xing B, Gao R, et al. Pan-cancer single-cell landscape of tumor-infiltrating T cells. Science 2021;374:abe6474.
14. Cheng S, Li Z, Gao R, Xing B, Gao Y, Yang Y, et al. A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. Cell 2021;184: 792–809.e23.
15. Tang F, Li J, Qi L, Liu D, Bo Y, Qin S, et al. A pan-cancer single-cell panorama of human natural killer cells. Cell 2023;186:4235–51.e20.
16. Zhang Y, Chen H, Mo H, Hu X, Gao R, Zhao Y, et al. Single-cell analyses reveal key immune cell subsets associated with response to PD-L1 blockade in triple-negative breast cancer. Cancer Cell 2021;39: 1578–93.e8.