HUMAN VACCINES & IMMUNOTHERAPEUTICS
2024, VOL. 20, NO. 1, 2318815
https://doi.org/10.1080/21645515.2024.2318815

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS Check for updates

# Immune regulation and the tumor microenvironment in anti-PD-1/PDL-1 and anti-CTLA-4 therapies for cancer immune evasion: A bibliometric analysis

Yi Huang[a,b,c*], Zhijian Chen[a,b,c*], Gang Shen[d*], Shuogui Fang[e], Junjiong Zheng[a,b,c], Zepai Chi[f], Yuanfeng Zhang[f], Yitong Zou[a,b,c], Qinghua Gan[a,b,c], Chengxiao Liao[a,b,c], Yuhui Yao[a,b,c], Jianqiu Kong[a,b,c], and Xinxiang Fan[a,b,c]

[a]Department of Urology, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, P. R. China; [b]Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, P. R. China; [c]Guangdong Provincial Clinical Research Center for Urological Diseases, Sun Yat-Sen University, Guangzhou, P. R. China; [d]Department of Urology, DUSHU Lake Hospital Affiliated to Soochow University, Suzhou, China; [e]Department of Radiotherapy, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, Guangdong, P. R. China; [f]Department of urology, Shantou Central Hospital, Shantou, China

**ABSTRACT**

This study aims to conduct a bibliometric analysis, employing visualization tools to examine literature pertaining to tumor immune evasion related to anti-CTLA-4 and anti-PD-1/PD-L1 therapy from 1999 to 2022. A special emphasis is placed on the interplay between tumor microenvironment, signaling pathways, immune cells and immune evasion, with data sourced from the Web of Science core collection (WoSCC). Advanced tools, including VOSviewer, Citespace, and Scimago Graphica, were utilized to analyze various parameters, such as co-authorship/co-citation patterns, regional contributions, journal preferences, keyword co-occurrences, and significant citation bursts. Out of 4778 publications reviewed, there was a marked increase in research focusing on immune evasion, with bladder cancer being notably prominent. Geographically, China, the USA, and Japan were the leading contributors. Prestigious institutions like MD Anderson Cancer Center, Harvard Medical School, Fudan University, and Sun Yat Sen University emerged as major players. Renowned journals in this domain included Frontiers in Immunology, Cancers, and Frontiers in Oncology. Ehen LP and Wang W were identified as prolific authors on this topic, while Topalian SL stood out as one of the most cited. Research current situation is notably pivoting toward challenges like immunotherapy resistance and the intricate signaling pathways driving drug resistance. This bibliometric study seeks to provide a comprehensive overview of past and current research trends, emphasizing the potential role of tumor microenvironment, signaling pathways and immune cells in the context of immune checkpoint inhibitors (ICIs) and tumor immune evasion.

**ARTICLE HISTORY**
Received 17 November 2023
Revised 26 January 2024
Accepted 11 February 2024

**KEYWORDS**
Immune checkpoint inhibitors (ICIs); PD-1/PD-L1; CLTA-4; immune evasion; bibliometrics

## Introduction

Cancer, a daunting global menace, is projected to witness an alarming escalation in cases, nearly surging by 50% from 2020 to 2040.[1] Over the span of decades, relentless research endeavors have unraveled multifaceted mechanisms driving cancer and have sculpted diverse treatment avenues. To date, surgery, chemotherapy and radiotherapy are recognized worldwide for cancer treatment.[2–4] Additionally, an increasing number of treatment methods, such as targeted therapy, photothermal therapy and photodynamic therapy,[5,6] are being developed and accepted. Yet, the landscape witnessed a transformative shift with the dawn of tumor immunotherapy, spotlighting ICIs as the beacon of hope.[7]

Immune checkpoint inhibitors (ICIs) are one of the most significant immunotherapy. Although chemotherapy and radiotherapy are still the main treatments for most cancer types, ICIs have been applied to a variety of solid and liquid tumors with promising results, providing a glimmer of hope for many tumors that currently have no good treatment options. ICIs, by judiciously targeting specific lymphocyte receptors or their ligands, aim to harness the body's innate anti-tumor potential.[8,9] Ipilimumab, the first antibody against cytotoxic T lymphocyte-associated protein 4 (CTLA-4), was introduced as a treatment for advanced melanoma in 2011.[10] The CTLA-4 antibody binds to CTLA-4 protein, disrupting the signaling pathways linked to the suppression of T cell activity, triggering T cells readily and enhancing the immune system's capacity to identify and eliminate cancer.[11] PD-1 (Programmed Death-1) and PD-L1 (Programmed Death Ligand-1) are two critical molecules on the cell membrane within the immune system, and their interaction plays a pivotal role in immune regulation and immune evasion.[12] By interrupting the interaction between PD-1/PD-L1 and T cells, Pembrolizumab or Atezolizumab alleviates the suppression of T cells, initiating T cell activation and bolstering the immune system's ability to mount a more robust attack against cancer cells. This mechanism unleashes the full potential of the immune response against cancer.[13,14]

However, the efficacy of these agents is often impeded by tumor immune evasion strategies, intricately woven with

**CONTACT** Jianqiu Kong kongjq5@mail.sysu.edu.cn; Xinxiang Fan fanxinx3@mail.sysu.edu.cn Department of Urology, Sun Yat-sen Memorial Hospital, Sun Yat-Sen University, 107 Yan Jiang West Road, Guangzhou 510120, People's Republic of China.
*Co-first authors.

the complexities of epigenetic and immune regulation.[15] The TME emerges as a crucible where cellular senescence, epigenetic shifts, and immune dynamics converge, influencing therapeutic outcomes.[16,17] Among the myriad factors, cellular senescence, characterized by cell cycle arrest and the Senescence-associated secretory phenotype (SASP), plays a pivotal role.[18] SASP, with its array of pro-inflammatory cytokines, can modify the TME, impacting tumor immunogenicity and the efficacy of ICIs. Epigenetic alterations, encompassing DNA methylation, histone modifications, and miRNA regulation, further sculpt the TME, influencing both adaptive and innate immune responses. Moreover, signaling pathways, like the c-Jun N-terminal kinase pathway, intricately link cellular senescence, epigenetic modifications, and immune responses, offering insights into potential therapeutic targets and strategies to overcome ICI resistance.[19]

Bibliometrics is a discipline which employs mathematical and statistical techniques to analyze scientific publications, providing valuable insights into research activity and academic communication. This bibliometric endeavor seeks to journey through the vast scientific literature, focusing on the interplay of cellular senescence, epigenetics, and immune evasion, especially in the context of anti-CTLA-4 and anti-PD-1/PD-L1 therapies. With a panoramic view of historical landmarks, current research niches, and prospective avenues, this study aims to inspire and guide future research trajectories, resonating with the themes of the special issue.

## Methods

### Data source and research ethics

For this study, we utilized the Science Citation Index Expanded (SCI-Expanded) from Clarivate Analytics' Web of Science Core Collection (WoSCC) as our primary data source. According to prior bibliometric studies, WoSCC is an extensively utilized and universally recognized database for academic and bibliometric research.[20,21] It encompasses thousands of high-impact journals and conference proceedings. Moreover, our research exclusively hinged on public databases, devoid of human subject involvement, thereby negating the need for ethical committee approval.

### Searching strategy

We retrieved the information of applicable literature on October 24, 2023. For the accuracy of the data, we finished the search within 1 day to avoid the data updates. The search criteria were as follows: topic = (cancer* OR tumor* OR tumor* OR oncology OR neoplasm* OR carcinoma*) AND topic = (PD-1 OR PD-L1 OR programmed cell death protein 1 ligand OR programmed cell death protein 1 OR cytotoxic T lymphocyte-associated antigen-4 OR CTLA-4) AND topic = (Immune) NEAR/1 (evasion OR escape OR avoidance OR resistance OR suppression) OR immunosuppression OR immunoevasion OR immunoescape OR immunoavoidance OR immunoresistance. A final product of 4778 publications were chosen for subsequent analysis after a more stringent selection process involving English-language articles and reviews from 1999 to 2022.

### Data analysis

Information regarding titles, keywords, abstracts, authors, institutions and reference records of the papers were downloaded, preserved and analyzed by two researchers independently, which could compare the analysis results to ensure the effectiveness of the data and the authenticity of the research. Microsoft Office Excel 2019 (Microsoft, Redmond, WA, USA) was applied to investigate the searched articles and exported the line charts and tables of top-productive or cited authors, coauthors, countries/regions, institutions, journals. Subsequently, a polynomial regression model was utilized to predict the publication counts for 2023, with the $R^2$ value serving as an indicator of prediction accuracy.

### Bibliometric analysis

VOSviewer (version 1.6.16), Citespace (version 5.8.R2) and SCImago Graphica (version 1.0.35) are frequently utilized to visualize the information and underlying connections of publications in bibliometric analysis. And VOSviewer provides three primary visual maps: time-overlay visualization map, the network visualization map and density visualization map.[22] In this study, we used VOSviewer to perform a visual analysis of organizations, journals, authors/co-cite authors, reference and keywords. While SCImago Graphic assessed international collaborations, Citespace pinpointed the 25 most salient keywords based on citation bursts.

## Results

### Trend of annual publications and citations

A total of 4778 papers were collected according to the searching strategy from 1999 to 2022. It could be seen from Figure 1 that the number of publications and citations have annually increased. In particular, the annual publication volume has increased sharply and exceeded 100 since 2015. As of the search date, the number of citations for all articles was 307,071, with a normal of 64.27 citations per thing. The increase in the quantity of annual publications and annual citations indicates that the researchers are devoting increasing energy to further study in this field. After the polynomial curve fitting of publication growth (Figure 1), there was a statistically significant correlation between publications and the published year of articles ($R^2 = 0.9877$). We can expect that the number of publications in 2023 is almost equal to 1200.

### Analysis of active countries/regions

There are 82 countries and regions, which had participated in the publication of relevant articles. Table 1 shows the top 10 countries in the number of publications, indicating that the China ranks first in the number of publications with 1801 articles published, followed by USA (1694), Japan (323), Germany (314) and Italy (272).

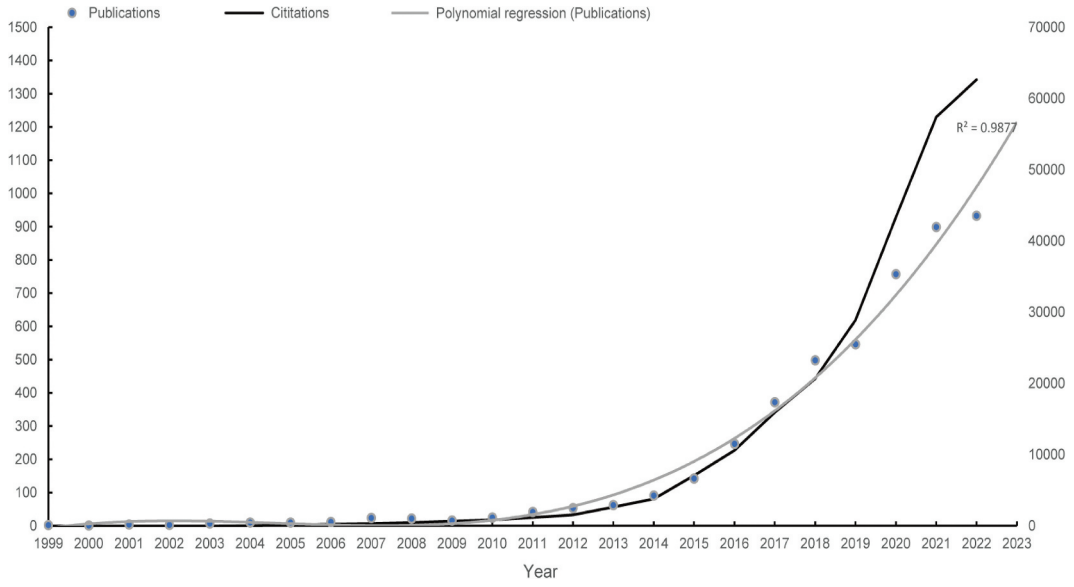


**Figure 1.** Annual publication and citation trends on tumor immune escape related to anti-CTLA-4 and anti-PD from 1999 to 2023. The left vertical axis denotes the annual publication count, whereas the right vertical axis represents the annual citation frequency. Blue dots correspond to the number of articles published each year, with the light black curve depicting the polynomial regression trend. The correlation coefficient ($R^2$) is provided within the figure.

**Table 1.** Top 10 productive countries/regions concerning the research of anti-CTLA-4 and anti-PD related tumor immune escape.

| Rank | Country/regions | Count | Total citations | H-index | Average citation per paper |
|---|---|---|---|---|---|
| 1 | China | 1801 | 66095 | 108 | 36.7 |
| 2 | USA | 1694 | 190935 | 194 | 112.71 |
| 3 | Japan | 323 | 23082 | 74 | 71.46 |
| 4 | Germany | 314 | 25848 | 73 | 82.32 |
| 5 | Italy | 272 | 14851 | 59 | 54.6 |
| 6 | United Kingdom | 212 | 19488 | 62 | 91.92 |
| 7 | France | 197 | 23286 | 56 | 118.2 |
| 8 | Australia | 148 | 12859 | 48 | 86.69 |
| 9 | South Korea | 137 | 6657 | 39 | 48.59 |
| 10 | Canada | 124 | 8879 | 48 | 71.6 |

Furthermore, USA also ranked first in total citations (190,935) and H index (194). It is worth noting that the average citations per paper in China ranks the bottom among the top 10 countries, but the number of publications ranks the first. In addition, we can see the trend of the top 10 countries from 1999 to 2022 on Figure 2a, which indicates the number of publications in most of the top 10 countries has risen steadily. In particular, China ‘s publications exceeds that of the United States, and the gap between them is increasing year by year from 2019 to 2022, indicating that China will dominate the number of publications in this field in the near future. When it comes to cooperation, SCImago Graphic is used to create a visual map of cooperation between countries and regions, in which the number of publications and the total link strength (TLS) are represented by notes size and the color of the connection (Figure 2b), respectively. And the thicker the line, the stronger the cooperative. Obviously, the cooperation between American and other countries is exceedingly closed.

## *Top 10 institutions and journals*

The top 10 most productive institutions in this field are shown in Table 2. MD Anderson ranked first with 168 articles published, followed by Fudan University (136), Harvard Medical School (134) and Sun Yat Sen University (118), indicating that USA and China play an important role in this field. But MD Anderson ‘s total citations are not the most. Among the top 10 institutions, Dana-Farber Cancer Institute, USA, has the most total citations (32720), which had published 105 articles in this filed. From the result of Figure 3, the cooperation between European and American institutions is closer, while that between other different international institutions is more dispersed. In addition, MD Anderson holds a significant position in the cooperation of institutions from different countries.

The top 10 active journals published a total of 1218 articles (Table 3), of which Frontiers in immunology holds 17.3% (211), followed by Cancers (14.4%) and Frontiers in oncology (10.8%) (Table 3). On the basis of 2022 Journal Citation Report (JCR), The impact factors of all the top 10 journals were higher than 5, of which seven were located in Q1, and the highest was Nature communications (IF 2022 = 17.694). It can be seen on Figure 4 that the cooperation among journals was relatively close.

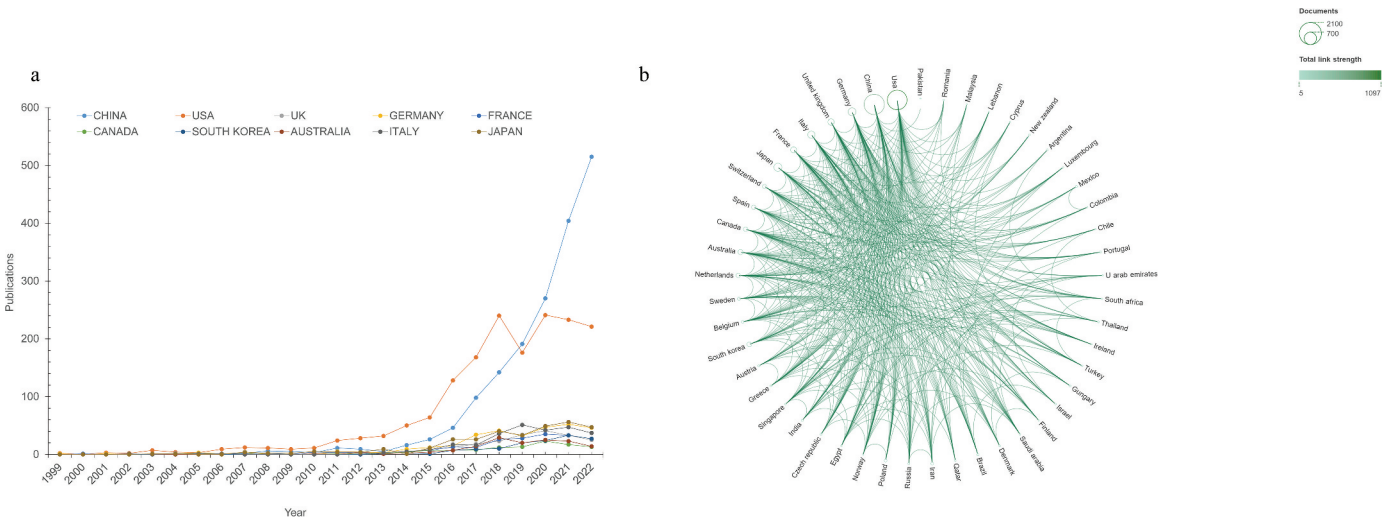


**Figure 2.** Visualization of annual publication trends and international collaborations from 1999 to 2023. (a) Annual publication trends for the top 10 contributing countries/regions. (b) A depiction of collaborations between countries/regions. Circle sizes correlate with a country's/region's publication count, while the circle color intensity signifies the total link strength.

**Table 2.** Top 10 institutes in the publications concerning the research of anti-CTLA-4 and anti-PD related tumor immune escape.

| Rank | Institutions | Countries/regions | Count | Total citations |
|---|---|---|---|---|
| 1 | MD Anderson | United States | 168 | 25678 |
| 2 | Fudan University | China | 136 | 6379 |
| 3 | Harvard Medical School | United States | 134 | 12842 |
| 4 | Sun Yat Sen University | China | 118 | 6325 |
| 5 | ShangHaiJiaoTong University | China | 117 | 4312 |
| 6 | Dana-Farber Cancer Institute | United States | 105 | 32720 |
| 7 | ZheJiang University | China | 88 | 2838 |
| 8 | university of chinese academy of sciences | China | 85 | 3552 |
| 9 | Memorial Sloan Kettering cancer center | United States | 80 | 26201 |
| 10 | China Medical University | China | 77 | 4145 |

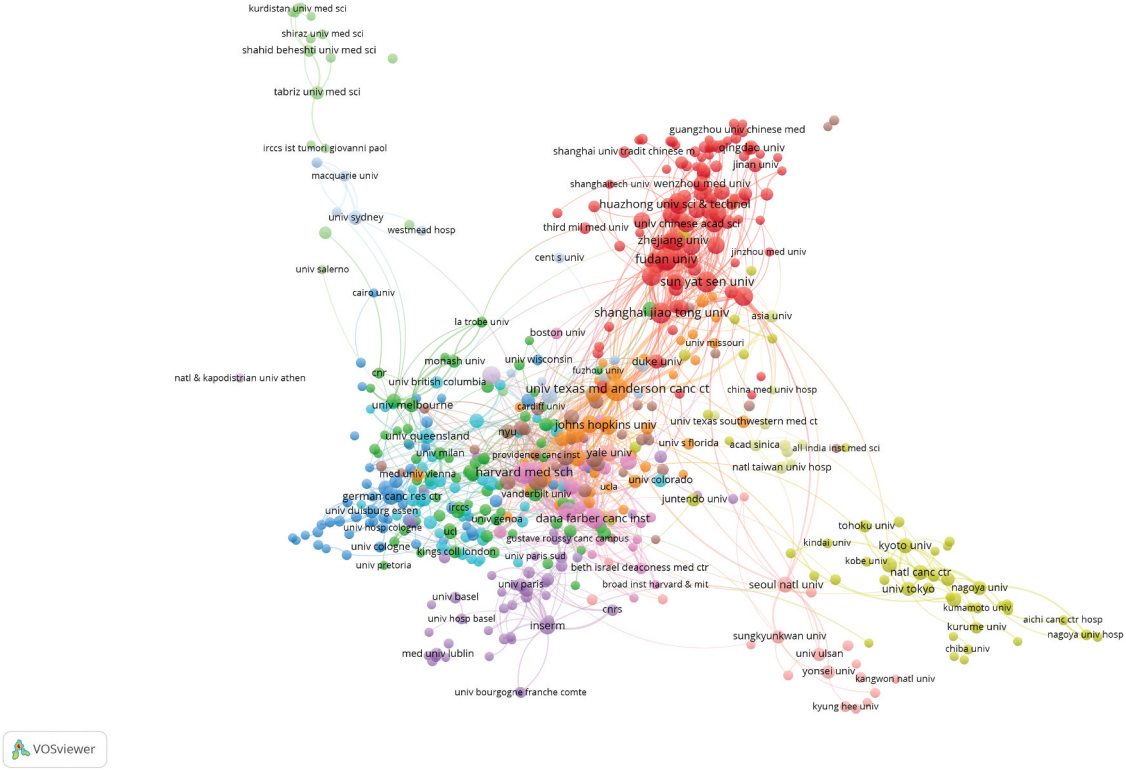


**Figure 3.** Inter-institutional collaboration network. Each node represents an institute, with node size indicating their publication volume. Nodes of the same color belong to the same category based on software classification, and the lines between institutions representing their collaborations.

**Table 3.** Top 10 journals in the publications concerning the research of anti-CTLA-4 and anti-PD related tumor immune escape.

| Rank | Journal title | Countries | Count | IF (2022) | JCR | Total citations |
|---|---|---|---|---|---|---|
| 1 | Frontiers in immunology | Switzerland | 211 | 8.786 | Q2 | 6767 |
| 2 | Cancers | Switzerland | 175 | 6.575 | Q2 | 3349 |
| 3 | Frontiers in oncology | Switzerland | 132 | 5.738 | Q2 | 2879 |
| 4 | Oncoimmunology | United States | 129 | 7.723 | Q1 | 6083 |
| 5 | Journal for immunotherapy of cancer | United States | 125 | 12.469 | Q1 | 7123 |
| 6 | Cancers immunology immunotherapy | United States | 102 | 6.63 | Q1 | 4674 |
| 7 | Clinical cancer research | United States | 98 | 13.801 | Q1 | 13547 |
| 8 | Cancer research | United States | 96 | 13.312 | Q1 | 11499 |
| 9 | International journal of molecular sciences | United States | 78 | 6.208 | Q1 | 1603 |
| 10 | Nature communications | England | 72 | 17.694 | Q1 | 5470 |

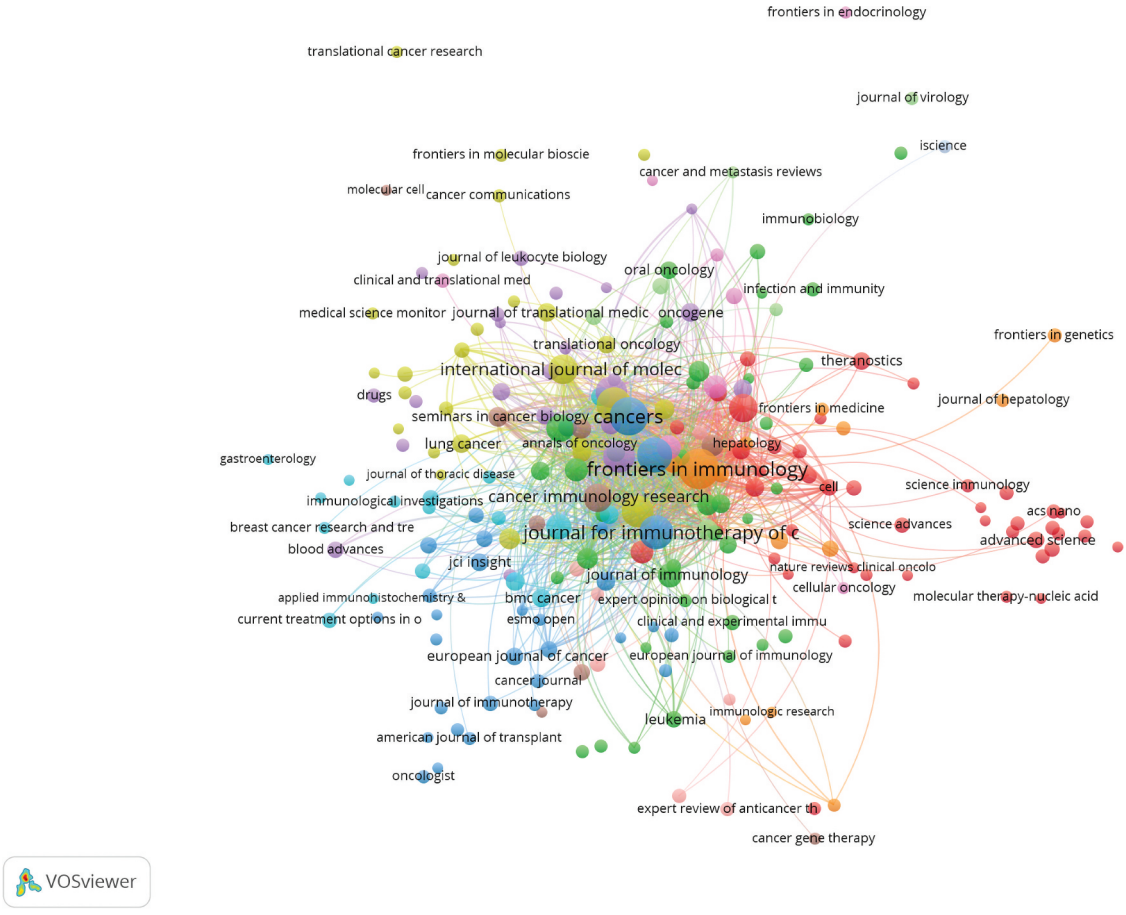


**Figure 4.** Journal collaboration network. Each node in this network diagram represents a scientific journal. The size of each node is proportional to the volume of publications that journal has contributed to the field of immunotherapy. Lines connecting the nodes illustrate the collaboration between journals. The thickness of these lines indicates the strength and frequency of the collaboration, with thicker lines signifying more frequent cross-citations or shared authorship.

### *Analysis of authors and co-cited authors*

Co-cited analysis can be applied to analyze the generation background, development overview and research frontier of a certain discipline which indicates that two authors or papers have a co-cited relationship, when the two authors or papers are published by a third author or paper. Among the authors of all articles published in this field, the 10 most productive authors and the top 10 coauthors are listed in Table 4. It is easy to find that the number of articles in the top 10 authors is not much different. The top three are Ehen LP (21), Wang W (20), Wang Y (19) and Zhang Y (19), of which more than half are Chinese scholars. Figure 5a shows that the cooperation between authors from different countries is weak. The above two phenomena indicate that researchers in this field have not yet carried out extensive cooperation, and the research is fragmented. Topalian SL (1454), Dong HD (926) and Brahmer JR (849) are the top three coauthors and a visualization map of co-cited authors is shown by Figure 5b. These results show that Topalian SL has strengthened collaboration with other authors and these authors are increasingly interested in further research in this field.

### *Analysis of co-citation references and keyword co-occurrence*

Co-citation references analysis can be used to visualize and evaluate the importance of different articles in different fields.

**Table 4.** The top 10 authors and the top 10 co-cited authors concerning the research of anti-CTLA-4 and anti-PD related tumor immune escape.

| Rank | Author | Count | Total citations | Co-cited author | Total citations |
|---|---|---|---|---|---|
| 1 | Chen LP | 21 | 5951 | Topalian SL | 1454 |
| 2 | Wang W | 20 | 914 | Dong HD | 926 |
| 3 | Wang Y | 19 | 1798 | Brahmer JR | 849 |
| 4 | Zhang Y | 19 | 993 | Sharma P | 779 |
| 5 | Wang J | 18 | 504 | Robert C | 767 |
| 6 | Zhang W | 18 | 498 | Ribas A | 747 |
| 7 | Freeman GJ | 17 | 9326 | Hodi FS | 699 |
| 8 | Huan MC | 17 | 2318 | Pardoll DM | 699 |
| 9 | Zhang L | 16 | 992 | Herbst RS | 666 |
| 10 | Liu Yang | 16 | 305 | Sparnger S | 625 |

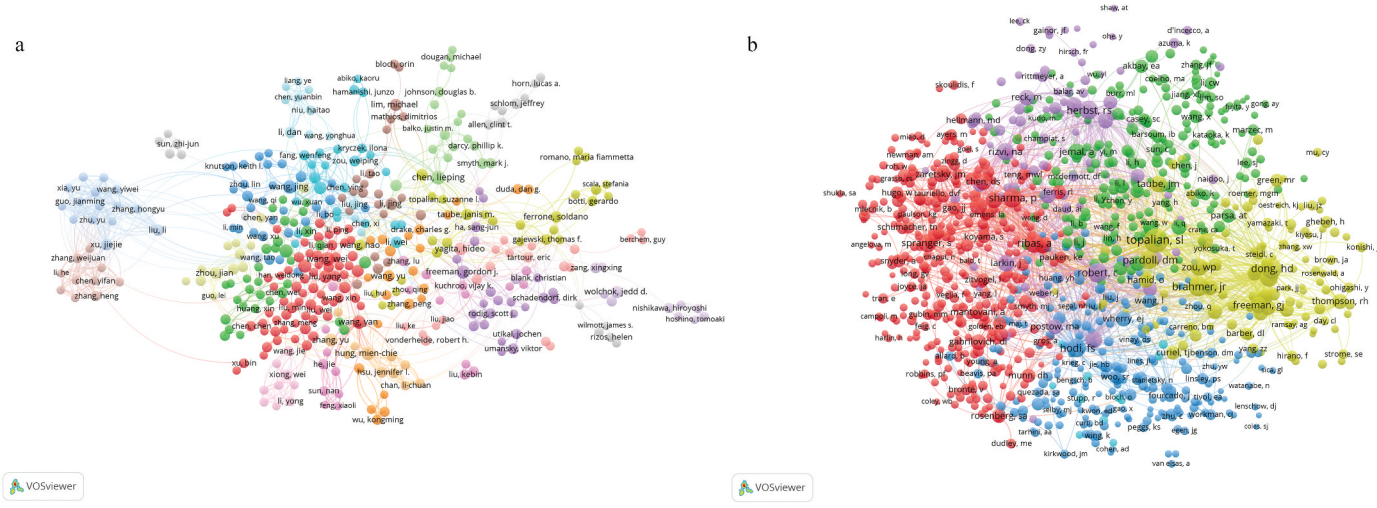


**Figure 5.** Analysis of authors and co-cited authors. Visualization map of co-authorship (a) and co-citation (b) analyses of authors generated by VOSviewer software.

The network visualization map of the co-cited references is shown in Figure 6. And a reference is represented by each circle. The frequency of citation increases with the size of the circle. From the papers obtained for our investigation, the connection between two circles reflects two references mentioned in the same article. Obviously, some articles had higher co-citation, such as Topalian Sl et al.[23] Hodi Fs et al.[24] Tumeh Pc et al.[25] and so on.

Keywords represent the subject content of the literature. Therefore, through keyword co-occurrence and burst analysis, it is helpful to reflect the research hotspots and grasp the development context of this field. The overlay visualization map of keyword co-occurrence using VOSviewer is shown in Figure 7a, in which the time sequence of keywords is represented by nodes of different colors. In the early stage, the more prominent keywords were "t cells," "ctla-4," "regulatory t cells" etc, which's notes were purple. And yellow nodes, such as "tumor microenvironment," "b7-h1 antigen," "ICIs," and "immunotherapy resistance," are emerging keywords, which have appeared frequently in recent years and may still be the focus of future research. Figure 7b listed top 25 keywords with the strongest citation brusts, where the red line is the period of occurrence. The early keywords were "b7family" (28.13), "b7 h1" (24.98) and "dendritic cells" (20.93). In particular, "b7family" is the longest keyword. In the past decade, a burst strength "safety" and "antibody" was both higher than 20. In addition to our comprehensive bibliometric analysis, we have also compiled a summary of common research mechanisms of immune evasion for immunotherapy in Table 5. This table encompasses a detailed overview of both molecular mechanisms and the related immune/stromal populations within the TME, offering a structured representation of the intricate dynamics at play in tumor immunology.

## Discussion

### *General information*

From 1999 to 2022, we observed a remarkable increase in the number of publications and citations relating to tumor immune evasion in the context of anti-CTLA-4 and anti-PD-1/PD-L1 therapies. This trend, highlighted by our bibliometric analysis, underscores the growing global interest and evolving understanding in this crucial area of cancer research. We predict a surge in publication volume, with an anticipated 1,200 articles by 2023, reflecting the intensified research focus in this domain.

The impact of immune checkpoint inhibitors (ICIs), such as anti-PD-1/PD-L1 and anti-CTLA-4, has been significant in improving cancer prognosis. However, the emergence of immune escape mechanisms continues to pose challenges, impacting patient survival and therapy effectiveness. Our analysis provides a rapid overview of the prevailing topics in this field, aiding researchers in navigating the expanding literature landscape.

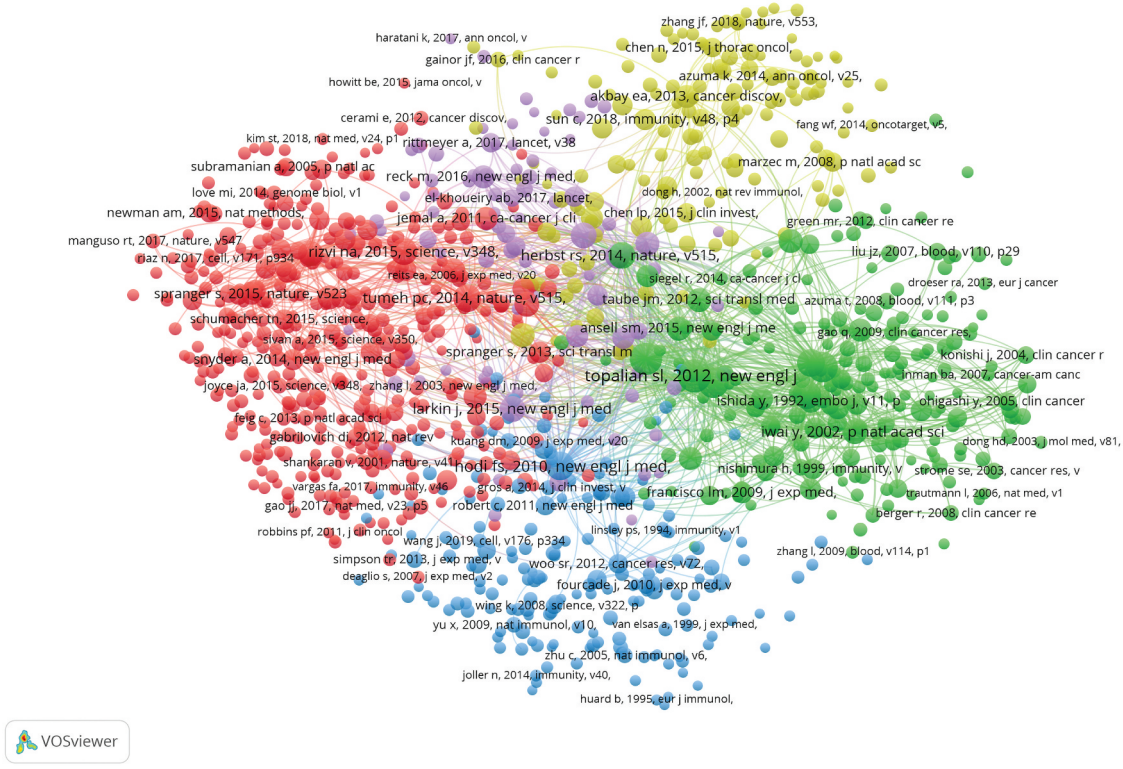


**Figure 6.** The network visualization maps of co-cited references were produced by VOSviewer.

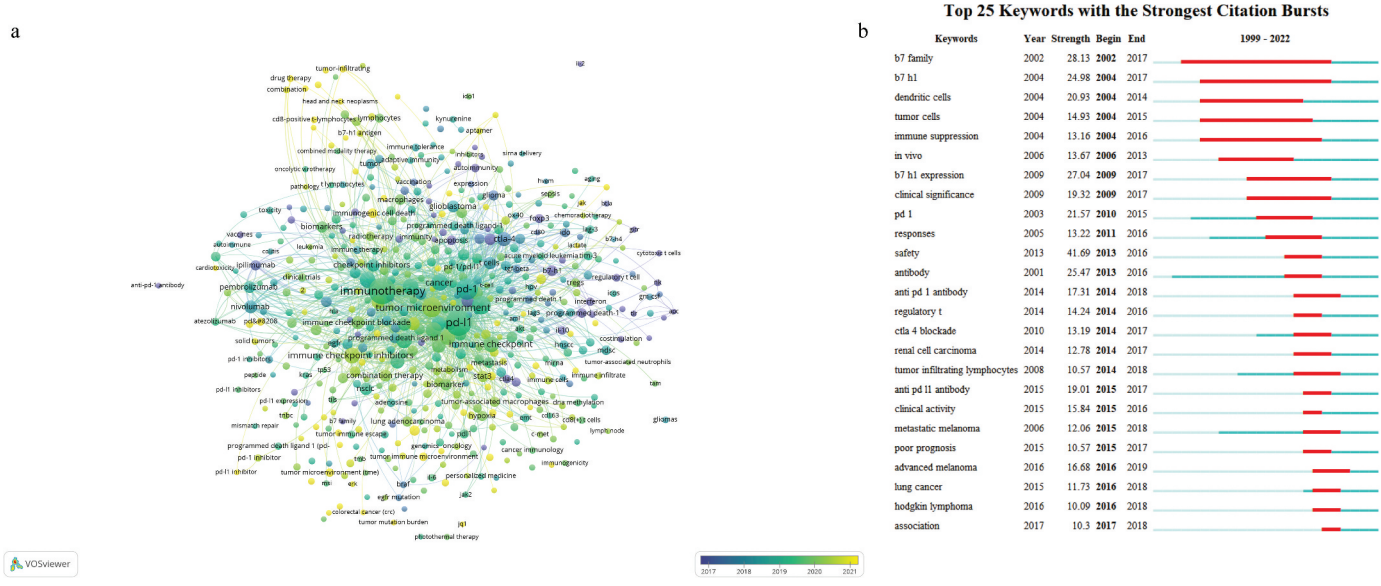


**Figure 7.** Keyword visualization and analysis. (a) A network visualization of keywords using VOSviewer, where node sizes grow with keyword frequency. (b) The 25 most frequently cited keywords pertinent to anti-CTLA-4 and anti-PD related tumor immune escape. The term "strength" refers to the connection intensity between two nodes, as determined by the software.

Our findings indicate China's increasing prominence in research publication volume, while the United States leads in total citations, H-index, and average citations per paper. This suggests the pivotal role of these countries in advancing research on tumor immune evasion related to anti-CTLA-4 and anti-PD therapies. Additionally, countries such as Japan, Germany, Italy, and the United Kingdom have made substantial contributions, each publishing over 200 articles in this area. Notably, Chinese institutions hold six positions in the top 10 most productive institutes, with the remaining four held by American institutions. This geographical distribution of contributions highlights the global collaborative efforts in researching ICIs and tumor immune evasion.

In our bibliometric analysis, we identified key contributors such as Chen LP from Yale University, whose research on fibrinogen-like protein 1 (FGL1) suggests its role in resistance to anti-PD-1/B7-H1 therapy and its potential as a prognostic marker in cancer.[26] Wang W's work provides insights into

**Table 5.** The commonly studied molecular mechanisms of immune evasions and immune/stromal populations of the TME.

| No | Molecular mechanism | Populations of TME |
|---|---|---|
| 1 | PD-1/PD-L1 | Tumor-Infiltrating Lymphocytes (TILs) |
| 2 | Tumor antigen loss | Tumor-Associated Fibroblasts (CAFs) |
| 3 | Histocompatibility Complex (MHC) Class I | Myeloid-Derived Suppressor Cells (MDSCs) |
| 4 | Cytokine Signaling Alterations | Tumor-Associated Macrophages (TAMs) |
| 5 | Indoleamine 2,3-dioxygenase (IDO) | Tumor Stem Cells |
| 6 | Antigen Presentation Pathway Alterations | Tumor-Associated Endothelial Cells |
| 7 | Exosome-Mediated Immune Suppression | Tumor-Associated Innate Immune Cells |
| 8 | Epigenetic Changes | Immune Checkpoint-Expressing Cells |
| 9 | Escape from Phagocytosis | Regulatory T cells (Tregs) |
| 10 | Mimicry of Host Molecules | Inflammatory Cells |

how HGF, MET amplification, and EGFR-T790M mutations contribute to PD-L1 expression in non-small cell lung cancer (NSCLC), facilitating immune evasion through distinct mechanisms.[27] Our analysis reveals key trends in tumor immunology, particularly focusing on "B7 family," "B7 h1" and "Dendritic cells" within the context of anti-CTLA-4 and anti-PD-1/PD-L1 therapies. The integration of these trends with molecular and cellular interactions in the TME, as detailed in Table 5, highlights the complexity of immune evasion and underscores the potential for novel therapeutic strategies to overcome resistance in cancer treatment.

Through these focused analyses, our study not only maps out the historical and current research landscape but also provides a foresight into the future directions, emphasizing the integral role of bibliometric analysis in understanding and advancing the field of tumor immunotherapy.

## *Immune evasion mechanisms*

Over the past two decades, immunotherapy has emerged as a cornerstone in cancer research, with the clinical application of ICIs marking a transformative shift in cancer therapeutics. However, the clinical challenge presented by tumor immune evasion, particularly in relation to anti-CTLA-4 and anti-PD-1/PD-L1 therapies, underscores a pressing need for solutions. Our bibliometric analysis highlights the prolific contributions from the United States in this domain, suggesting the imperative for bolstered international and institutional collaborations. As the research horizon expands, the safety and efficacy of ICIs, discovery of novel immune checkpoints, combination therapies, and the intricate signaling pathways governing drug resistance have ascended as paramount research foci.

Tumor immunotherapy, especially with ICIs, has been a beacon of hope in oncology. Yet, the labyrinth of tumor immune evasion mechanisms – shaped by intricate cellular senescence processes, epigenetic modifications, and immune regulations – casts shadows over the promise of these therapies. CTLA-4 is a consistent immune checkpoint receptor expressed on various T cells, exhibiting a high affinity for B7 molecules. The interaction between CTLA-4 and B7 molecules on APC effectively counteracts the costimulatory signal provided by T cell receptor (TCR) and/or CD28, thereby impeding T cell activation.[28] Consequently, the primary mechanism of action of CTLA-4 inhibitors is to antagonize the negative regulatory effect of CTLA-4 on T cell activation in order to enhance the immune response of T cells against tumors.[29] Furthermore, Simpson et al. demonstrated that anti-CTLA-4 treatment specifically depletes tumor microenvironment-resident Treg cells, which aligns with their findings in a preclinical model,[30] suggesting that depletion of immunosuppressive Treg cells may serve as an additional mechanism underlying the antitumor effect of CTLA-4 blockade. Lastly, antibody-dependent cell-mediated cytotoxicity (AD has also been validated as a potential mechanism contributing to its antitumor activity).[31]

PD-1 and PD-L1 are cell surface molecules primarily expressed on immune cells and tumor cells. The PD-1/PD-L1 pathway functions by inhibiting the phosphorylation of TCR activation signal CD28 and ZAP70, resulting in T cell exhaustion and evasion of the tumor immune response. Targeting this signaling axis with anti-PD-1 and PD-L1 antibodies aims to alleviate T-cell exhaustion, restore original function, and induce sustained high-frequency tumor responses.[32–35] Furthermore, PD-1 can also impact the proliferation, activation, cytokine production of T cells, as well as contribute to their exhaustion.[36] It is plausible that anti-PD-1 and PD-L1 therapies may impede this mechanism for treating tumors. Importantly, it should be noted that the underlying epigenetic alterations in exhausted phenotype T cells were not restored.[37]

The success of clinical transformation of anti-CTLA-4 and anti-PD therapy is a revolutionary change in cancer treatment. However, only a few tumors respond to anti-CTLA-4 and anti-PD-1/PD-L1 therapies, or even develop drug resistance shortly after treatment, leading to treatment failure. Therefore, the research on the mechanism of drug resistance is gradually becoming hot. Studies on the mechanism of drug resistance mainly focus on two aspects, the internal and external of tumor cells. Tumor cell-autonomous mechanisms of immune checkpoint blockade resistance are mostly genetically related. For example, B2M and HLA-alleles are components of MHC-I molecules required for antigen presentation,[38] and their deletions and deleterious alterations have been found in ICI-resistant cancer patients.[39–42] Similarly, the loss of phosphatase and tensin homolog (PTEN) can also promote ICIs resistance,[43] which may be related to the up-regulation of immunosuppressive cytokines including VEGF and the increase of DKK2 expression. It has been reported that administration of DKK2 in established mouse models inhibited the increase in CD8 tumor-infiltrating lymphocytes and the activation of NK and CD8 T cells induced by anti-PD-1

therapy.[44] In addition, alterations in chromosome region 9p24.1 in Hodgkin's lymphoma can induce the expression of PD-1 ligands through Janus kinase (JAK) -signal transducer and activator of transcription (STAT) signaling,[45] promoting tumor immune escape. Furthermore, activation of the oncogenic Wnt-β-catenin signaling pathway in tumor cells can inhibit the chemokine CCL4, leading to reduced recruitment of tumor-infiltrating T cells and subsequent failure of T cell activation,[46] which is also considered to be one of the mechanisms of ICIs resistance. The cellular dance of CTLA-4 and PD-1/PD-L1, pivotal in T-cell activation and exhaustion, has direct implications on the therapeutic outcomes. Yet, beyond these molecular interactions, the realm of epigenetics, particularly DNA methylation patterns and histone modifications, has profound impacts on cellular senescence, and in turn, the efficacy of ICIs. For instance, the epigenetic landscape, characterized by the likes of methylation and acetylation, dictates the transcriptional fates of genes pivotal for cellular senescence and immune responses.

The tumor microenvironment (TME) emerges as a complex tapestry where cancer cells, stromal cells, immune cells, and extracellular matrix intermingle.[47] Within this milieu, cellular senescence, driven by the likes of the Wnt signaling pathway and influenced by epigenetic shifts, shapes the immune landscape.[48] Furthermore, interferon-dependent activation of senescence-inducing cell cycle regulators is capable of preventing cancer cells from escaping the immune system by controlling the cell cycle routes.[49] Tryptophan catabolism within the TME has been proposed as a mechanism for suppressing anti-tumor immune responses. This process generates immunosuppressive metabolites and depletes essential amino acid tryptophan, thereby inhibiting clonal proliferation of T cells.[50] Given that T cells play a crucial role in the body's immune function, their decline contributes to the challenge in understanding the failure of anti-CTLA-4 and anti-PD therapy. Additionally, regulatory T (Treg) cells, Th2 cells, and myeloid-derived suppressor cells (MDSCs) within the TME hinder CTL and Th1 cell responses induced by anti-CTLA-4 and anti-PD treatment,[51] which are vital for mounting an effective anti-tumor response. Similarly, stromal cells within the TME exert control over migration of T cells from circulation into tumors through mechanisms that prevent direct interaction between these immune effector cells and cancerous counterparts.[52] It should be noted that resistance mechanisms extend beyond the confines of the tumor microenvironment. Alterations in patients' intestinal microbiome have also been associated with response and resistance to anti-CTLA-4 and anti-PD treatment,[53] although specific underlying mechanisms remain unknown.

In exploring the mechanisms underlying resistance to immune checkpoint inhibitors (ICIs), significant focus has been directed toward non-small cell lung cancer (NSCLC) and melanoma, given their prevalence and unique immunological characteristics. In NSCLC research, studies have highlighted the role of tumor-specific or bystander tissue-resident memory (TRM)-like cells.[54] Prior to tumor onset, these cells can enhance immune cell recruitment, leading to an immune evasion mechanism characterized by the loss of MHC class I protein expression and subsequent resistance to immune checkpoint inhibitors. This finding underscores the complex interplay between tumor microenvironment and immune response, providing critical insights into NSCLC immune evasion strategies.

Melanoma research has similarly yielded crucial discoveries, such as the work of YiX et al., which demonstrates how SIRT7 contributes to melanoma progression. SIRT7's role in enhancing tumor cell survival and facilitating immune evasion through the unfolded protein response pathway reveals important aspects of melanoma's ability to evade immune surveillance.[55]

Further research, including studies by Peranzoni et al., expands our understanding of immune evasion.[56] For instance, they discovered that macrophages can impede CD8 T cell infiltration into tumor cells, thus limiting the effectiveness of anti-PD-1 therapy. Similarly, Ma et al. have shown that hypoxia in triple-negative breast cancer induces chromatin remodeling, suppressing immune effector gene expression in T and NK cells and reducing their cytotoxicity and interferon signaling response.[57] Liu et al.'s findings on CircQSOX1's role in promoting Treg cell infiltration in colorectal cancer further illustrate the diverse mechanisms of immune evasion across different tumor types.[58] These studies collectively highlight the intricate relationship between cellular senescence, epigenetic modifications, and immune responses within the tumor microenvironment (TME), laying the groundwork for understanding the challenges in enhancing the efficacy of anti-CTLA-4 and anti-PD therapies.

As our understanding deepens regarding the underlying mechanisms behind drug resistance, treatment approaches are continuously emerging. One such approach involves combining two ICIs, which has been approved by the US FDA for metastatic melanoma treatment despite its unique adverse effects. The clinical value of combining ICIs with other immune stimulating cytokines or agonists is also being investigated. Furthermore, researchers are exploring ways to enhance ICIs immunotherapy and prevent immunotherapy escape by manipulating the tumor microenvironment (TME) and intestinal flora through adjuvant microbial agents or microbiome manipulation.[59,60] Several drugs targeting ICIs resistance have already demonstrated efficacy. For instance, stromal cells within the TME can impede direct interaction between T cells and cancer cells, resulting in immunotherapy failure. Epigenetic silencing of genes encoding chemokines Cxcl9 and Cxcl10 is one example.[61] However, treatment with epigenetic modulators has shown promise in enhancing anti-PD-L1 therapy effectiveness.[62] The interplay between cellular senescence, epigenetics, and immune responses, especially within the TME, underscores the need for a holistic approach to unlock the full potential of ICIs in cancer therapeutics.

## Limitations

Firstly, bibliometric studies often focus on English literature, potentially overlooking valuable contributions from studies

written in other languages. Moreover, due to the intricate and time-consuming nature of collecting and analyzing citation data, our bibliometric approach might not capture the very latest developments in the field, particularly those emphasizing the intersections of cellular senescence, epigenetics, and immune regulations in the context of tumor immunotherapy.

## Conclusion

Our bibliometric analysis of tumor immune escape, especially against PD-1/PD-L1 and CTLA4, underscores the dynamic and rapidly evolving nature of this research domain. As we delve deeper into understanding the multifaceted mechanisms of tumor immune escape, we begin to see the profound influences of cellular senescence and epigenetic changes in shaping the immune landscape. This enhanced understanding is pivotal in designing and optimizing immunotherapy strategies, ultimately aiming to improve therapeutic outcomes for tumors. Our findings not only chart the historical and current trajectories of tumor immunotherapy but also emphasize the importance of cellular senescence, epigenetics, and immune responses in this arena. As we move forward, future research will undoubtedly uncover novel therapeutic targets and strategies, addressing immune evasion more effectively, and promising enhanced treatment outcomes and better quality of life for patients.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Funding

This work was supported by the National Natural Science Foundation of China (82002682, 82203720), the Science and Technology Planning Project of Guangdong Province (2020A1515111119, 2019A1515010188) and the Guangzhou Municipal Basic Research Program Jointly Funded by City, University, and Enterprise Special Project (2024A03J0907).

## Data availability statement

Upon reasonable request, the corresponding author will make available the data sets used and/or analyzed during the current work.

## Author contributions

JZ, XF and JK conceived the study. YH, ZC, and SF collected the data and wrote the manuscript. GS, ZC, YZ, YZ, CL, QG and YY revised and reviewed the manuscript. All authors contributed to the article and approved the submitted version.

## Ethics statement

The data of our study were obtained from public databases. Ethics committee permission was not required.

## References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71:209–49. doi:10.3322/caac.21660.
2. Wyld L, Audisio RA, Poston GJ. The evolution of cancer surgery and future perspectives. Nat Rev Clin Oncol. 2015;12(2):115–24. doi:10.1038/nrclinonc.2014.191.
3. Galmarini D, Galmarini CM, Galmarini FC. Cancer chemotherapy: a critical analysis of its 60 years of history. Crit Rev Oncol Hematol. 2012;84(2):181–99. doi:10.1016/j.critrevonc.2012.03.002.
4. Schaue D, McBride WH. Opportunities and challenges of radiotherapy for treating cancer. Nat Rev Clin Oncol. 2015;12(9):527–40. doi:10.1038/nrclinonc.2015.120.
5. Baudino TA. Targeted cancer therapy: the next generation of cancer treatment. Curr Drug Discov Technol. 2015;12(1):3–20. doi:10.2174/1570163812666150602144310.
6. Li X, Lovell JF, Yoon J, Chen X. Clinical development and potential of photothermal and photodynamic therapies for cancer. Nat Rev Clin Oncol. 2020;17(11):657–74. doi:10.1038/s41571-020-0410-2.
7. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science (New York, NY). 2013;342:1432–3. doi:10.1126/science.342.6165.1432.
8. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–64. doi:10.1038/nrc3239.
9. Sharma P, Allison JP. The future of immune checkpoint therapy. Science (New York, NY). 2015;348(6230):56–61. doi:10.1126/science.aaa8172.
10. Korman AJ, Garrett-Thomson SC, Lonberg N. The foundations of immune checkpoint blockade and the ipilimumab approval decennial. Nat Rev Drug Discov. 2022;21(7):509–28. doi:10.1038/s41573-021-00345-8.
11. Carlino MS, Larkin J, Long GV. Immune checkpoint inhibitors in melanoma. Lancet (London, England). 2021;398:1002–14. doi:10.1016/s0140-6736(21)01206-x.
12. Bagchi S, Yuan R, Engleman EG. Immune checkpoint inhibitors for the treatment of cancer: clinical impact and mechanisms of response and resistance. Annu Rev Pathol. 2021;16(1):223–49. doi:10.1146/annurev-pathol-042020-042741.
13. Kwok G, Yau TC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). Hum Vaccines Immunother. 2016;12(11):2777–89. doi:10.1080/21645515.2016.1199310.
14. Willsmore ZN, Coumbe BGT, Crescioli S, Reci S, Gupta A, Harris RJ, Chenoweth A, Chauhan J, Bax HJ, McCraw A, et al. Combined anti-PD-1 and anti-CTLA-4 checkpoint blockade: treatment of melanoma and immune mechanisms of action. Eur J Immunol. 2021;51(3):544–56. doi:10.1002/eji.202048747.
15. Drake CG, Jaffee E, Pardoll DM. Mechanisms of immune evasion by tumors. Adv Immunol. 2006;90:51–81. doi:10.1016/s0065-2776(06)90002-9.
16. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. 2009;458(7239):719–24. doi:10.1038/nature07943.
17. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol. 2008;8(6):467–77. doi:10.1038/nri2326.
18. Chibaya L, Murphy KC, DeMarco KD, Gopalan S, Liu H, Parikh CN, Lopez-Diaz Y, Faulkner M, Li J, Morris JP, et al. EZH2 inhibition remodels the inflammatory senescence-associated secretory phenotype to potentiate pancreatic cancer immune surveillance. Nat Cancer. 2023;4(6):872–92. doi:10.1038/s43018-023-00553-8.
19. Deng Y, Adam V, Nepovimova E, Heger Z, Valko M, Wu Q, Wei W, Kuca K. c-Jun N-terminal kinase signaling in cellular senescence. Arch Toxicol. 2023;97:2089–109. doi:10.1007/s00204-023-03540-1.
20. Deng S, Meng F, Wang L, Yang Z, Xuan L, Xuan Z, Wang J. Global research trends in non-muscle invasive bladder cancer: bibliometric and visualized analysis. Front Oncol. 2022;12:1044830. doi:10.3389/fonc.2022.1044830.

21. Ma C, Su H, Li H. Global research trends on prostate diseases and erectile dysfunction: a bibliometric and visualized study. Front Oncol. 2020;10:627891. doi:10.3389/fonc.2020.627891.
22. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. 2010;84:523–38. doi:10.1007/s11192-009-0146-3.
23. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med. 2012;366:2443–54. doi:10.1056/NEJMoa1200690.
24. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23. doi:10.1056/NEJMoa1003466.
25. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, Chmielowski B, Spasic M, Henry G, Ciobanu V, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014;515(7528):568–71. doi:10.1038/nature13954.
26. Wang J, Sanmamed MF, Datar I, Su TT, Ji L, Sun J, Chen L, Chen Y, Zhu G, Yin W, et al. Fibrinogen-like protein 1 Is a major immune inhibitory ligand of LAG-3. Cell. 2019;176:334–47 e12. doi:10.1016/j.cell.2018.11.010.
27. Peng S, Wang R, Zhang X, Ma Y, Zhong L, Li K, Nishiyama A, Arai S, Yano S, Wang W, et al. EGFR-TKI resistance promotes immune escape in lung cancer via increased PD-L1 expression. Mol Cancer. 2019;18(1):165. doi:10.1186/s12943-019-1073-4.
28. Walker LS, Sansom DM. Confusing signals: recent progress in CTLA-4 biology. Trends Immunol. 2015;36(2):63–70. doi:10.1016/j.it.2014.12.001.
29. Kvistborg P, Philips D, Kelderman S, Hageman L, Ottensmeier C, Joseph-Pietras D, Welters MJP, van der Burg S, Kapiteijn E, Michielin O, et al. Anti–CTLA-4 therapy broadens the melanoma-reactive CD8 + T cell response. Sci Transl Med. 2014;6:254ra128. doi:10.1126/scitranslmed.3008918.
30. Simpson TR, Li F, Montalvo-Ortiz W, Sepulveda MA, Bergerhoff K, Arce F, Roddie C, Henry JY, Yagita H, Wolchok JD, et al. Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti–CTLA-4 therapy against melanoma. J Exp Med. 2013;210:1695–710. doi:10.1084/jem.20130579.
31. Selby MJ, Engelhardt JJ, Quigley M, Henning KA, Chen T, Srinivasan M, Korman AJ. Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. Cancer Immunol Res. 2013;1:32–42. doi:10.1158/2326-6066.Cir-13-0013.
32. Hofmeyer KA, Jeon H, Zang X. The PD-1/PD-L1 (B7-H1) pathway in chronic infection-induced cytotoxic T lymphocyte exhaustion. J Biomed Biotechnol. 2011;2011:451694. doi:10.1155/2011/451694.
33. Patsoukis N, Duke-Cohan JS, Chaudhri A, Aksoylar HI, Wang Q, Council A, Berg A, Freeman GJ, Boussiotis VA. Interaction of SHP-2 SH2 domains with PD-1 ITSM induces PD-1 dimerization and SHP-2 activation. Commun Biol. 2020;3:128. doi:10.1038/s42003-020-0845-0.
34. Pauken KE, Wherry EJ. Overcoming T cell exhaustion in infection and cancer. Trends Immunol. 2015;36(4):265–76. doi:10.1016/j.it.2015.02.008.
35. Xu N, Guo R, Yang X, Li N, Yu J, Zhang P. Exosomes-mediated tumor treatment: one body plays multiple roles. Asian J Pharm Sci. 2022;17(3):385–400. doi:10.1016/j.ajps.2021.08.003.
36. Patsoukis N, Brown J, Petkova V, Liu F, Li L, Boussiotis VA. Selective effects of PD-1 on Akt and Ras pathways regulate molecular components of the cell cycle and inhibit T cell proliferation. Sci Signal. 2012;5(230):ra46. doi:10.1126/scisignal.2002796.
37. Benci JL, Xu B, Qiu Y, Wu TJ, Dada H, Twyman-Saint Victor C, Cucolo L, Lee DSM, Pauken KE, Huang AC, et al. Tumor interferon signaling regulates a multigenic resistance program to immune checkpoint blockade. Cell. 2016;167(6):1540–54.e12. doi:10.1016/j.cell.2016.11.022.
38. Rooney MS, Shukla SA, Wu CJ, Getz G, Hacohen N. Molecular and genetic properties of tumors associated with local immune cytolytic activity. Cell. 2015;160(1–2):48–61. doi:10.1016/j.cell.2014.12.033.
39. Gettinger S, Choi J, Hastings K, Truini A, Datar I, Sowell R, Wurtz A, Dong W, Cai G, Melnick MA, et al. Impaired HLA class I antigen processing and presentation as a mechanism of acquired resistance to immune checkpoint inhibitors in lung cancer. Cancer Discov. 2017;7(12):1420–35. doi:10.1158/2159-8290.Cd-17-0593.
40. McGranahan N, Rosenthal R, Hiley CT, Rowan AJ, Watkins TBK, Wilson GA, Birkbak NJ, Veeriah S, Van Loo P, Herrero J, et al. Allele-specific HLA loss and immune escape in lung cancer evolution. Cell. 2017;171(6):1259–71.e11. doi:10.1016/j.cell.2017.10.001.
41. Sade-Feldman M, Jiao YJ, Chen JH, Rooney MS, Barzily-Rokni M, Eliane JP, Bjorgaard SL, Hammond MR, Vitzthum H, Blackmon SM, et al. Resistance to checkpoint blockade therapy through inactivation of antigen presentation. Nat Commun. 2017;8(1):1136. doi:10.1038/s41467-017-01062-w.
42. Zaretsky JM, Garcia-Diaz A, Shin DS, Escuin-Ordinas H, Hugo W, Hu-Lieskovan S, Torrejon DY, Abril-Rodriguez G, Sandoval S, Barthly L, et al. Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med. 2016;375(9):819–29. doi:10.1056/NEJMoa1604958.
43. Peng W, Chen JQ, Liu C, Malu S, Creasy C, Tetzlaff MT, Xu C, McKenzie JA, Zhang C, Liang X, et al. Loss of PTEN promotes resistance to T cell–mediated immunotherapy. Cancer Discovery. 2016;6:202–16. doi:10.1158/2159-8290.Cd-15-0283.
44. Xiao Q, Wu J, Wang WJ, Chen S, Zheng Y, Yu X, Meeth K, Sahraei M, Bothwell ALM, Chen L, et al. DKK2 imparts tumor immunity evasion through β-catenin-independent suppression of cytotoxic immune-cell activation. Nat Med. 2018;24(3):262–70. doi:10.1038/nm.4496.
45. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, Schuster SJ, Millenson MM, Cattry D, Freeman GJ, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311–9. doi:10.1056/NEJMoa1411087.
46. Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity. Nature. 2015;523(7559):231–5. doi:10.1038/nature14404.
47. Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell. 2012;21(3):309–22. doi:10.1016/j.ccr.2012.02.022.
48. Warde KM, Smith LJ, Liu L, Stubben CJ, Lohman BK, Willett PW, Ammer JL, Castaneda-Hernandez G, Imodoye SO, Zhang C, et al. Senescence-induced immune remodeling facilitates metastatic adrenal cancer in a sex-dimorphic manner. Nat Aging. 2023;3(7):846–65. doi:10.1038/s43587-023-00420-2.
49. Brenner E, Schörg BF, Ahmetlić F, Wieder T, Hilke FJ, Simon N, Schroeder C, Demidov G, Riedel T, Fehrenbacher B, et al. Cancer immune control needs senescence induction by interferon-dependent cell cycle regulator pathways in tumours. Nat Commun. 2020;11(1):1335. doi:10.1038/s41467-020-14987-6.
50. Platten M, Wick W, Van den Eynde BJ. Tryptophan catabolism in cancer: beyond IDO and tryptophan depletion. Cancer Res. 2012;72(21):5435–40. doi:10.1158/0008-5472.Can-12-0569.
51. Coussens LM, Zitvogel L, Palucka AK. Neutralizing tumor-promoting chronic inflammation: a magic bullet? Science (New York, NY). 2013;339(6117):286–91. doi:10.1126/science.1232227.
52. Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science (New York, NY). 2015;348(6230):74–80. doi:10.1126/science.aaa6204.
53. Gopalakrishnan V, Helmink BA, Spencer CN, Reuben A, Wargo JA. The influence of the gut microbiome on cancer,

immunity, and cancer immunotherapy. Cancer Cell. 2018;33 (4):570–80. doi:10.1016/j.ccell.2018.03.015.
54. Weeden CE, Gayevskiy V, Marceaux C, Batey D, Tan T, Yokote K, Ribera NT, Clatch A, Christo S, Teh CE, et al. Early immune pressure initiated by tissue-resident memory T cells sculpts tumor evolution in non-small cell lung cancer. Cancer Cell. 2023;41:837–52 e6. doi:10.1016/j.ccell.2023.03.019.
55. Yi X, Wang H, Yang Y, Wang H, Zhang H, Guo S, Chen J, Du J, Tian Y, Ma J, et al. SIRT7 orchestrates melanoma progression by simultaneously promoting cell survival and immune evasion via UPR activation. Signal Transduct Target Ther. 2023;8:107. doi:10.1038/s41392-023-01314-w.
56. Peranzoni E, Lemoine J, Vimeux L, Feuillet V, Barrin S, Kantari-Mimoun C, Bercovici N, Guérin M, Biton J, Ouakrim H, et al. Macrophages impede CD8 T cells from reaching tumor cells and limit the efficacy of anti–PD-1 treatment. Proc Natl Acad Sci USA. 2018;115:E4041–e50. doi:10.1073/pnas.1720948115.
57. Ma S, Zhao Y, Lee WC, Ong LT, Lee PL, Jiang Z, Oguz G, Niu Z, Liu M, Goh JY, et al. Hypoxia induces HIF1α-dependent epigenetic vulnerability in triple negative breast cancer to confer immune effector dysfunction and resistance to anti-PD-1 immunotherapy. Nat Commun. 2022;13(1):4118. doi:10.1038/s41467-022-31764-9.
58. Liu Z, Zheng N, Li J, Li C, Zheng D, Jiang X, Ge X, Liu M, Liu L, Song Z, et al. N6-methyladenosine-modified circular RNA QSOX1 promotes colorectal cancer resistance to anti-CTLA-4 therapy through induction of intratumoral regulatory T cells. Drug Resist Updat. 2022;65:100886. doi:10.1016/j.drup.2022.100886.
59. Li J, Jia H, Cai X, Zhong H, Feng Q, Sunagawa S, Arumugam M, Kultima JR, Prifti E, Nielsen T, et al. An integrated catalog of reference genes in the human gut microbiome. Nat Biotechnol. 2014;32(8):834–41. doi:10.1038/nbt.2942.
60. Nielsen HB, Almeida M, Juncker AS, Rasmussen S, Li J, Sunagawa S, Plichta DR, Gautier L, Pedersen AG, Le Chatelier E, et al. Identification and assembly of genomes and genetic elements in complex metagenomic samples without using reference genomes. Nat Biotechnol. 2014;32(8):822–8. doi:10.1038/nbt.2939.
61. Nagarsheth N, Peng D, Kryczek I, Wu K, Li W, Zhao E, Zhao L, Wei S, Frankel T, Vatan L, et al. PRC2 epigenetically silences Th1-type chemokines to suppress effector T-Cell trafficking in colon cancer. Cancer Res. 2016;76(2):275–82. doi:10.1158/0008-5472.Can-15-1938.
62. Peng D, Kryczek I, Nagarsheth N, Zhao L, Wei S, Wang W, Sun Y, Zhao E, Vatan L, Szeliga W, et al. Epigenetic silencing of TH1-type chemokines shapes tumour immunity and immunotherapy. Nature. 2015;527(7577):249–53. doi:10.1038/nature15520.