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Uncovering global research frontiers in deubiquitinating enzymes and immunotherapy: A bibliometric study

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ABSTRACT

Recently, immunotherapy has been a key therapeutic strategy for cancer. Deubiquitinating enzymes (DUBs), which are protein-modifying enzymes, have a crucial role in the pathogenesis of cancer, autoimmune diseases, and inflammation. DUBs influence the tumor immune microenvironment by regulating immune cell functions and key signaling pathways. Thus, the potential applications of DUBs in immunotherapy have piqued the interest of the scientific community. This study performed bibliometric analysis to comprehensively examine the research hotspots and trends in this field, providing theoretical foundations and guidance for future research. Studies associated with DUBs and immunotherapy conducted over a decade (2014 to 2024) were searched and extracted from Web of Science Collection database. The analysis was performed using CiteSpace, VOSviewer, and the Bibliometrix package in R software. Visualizations were generated for countries, institutions, authors, journals, references, and keyword co-occurrences. In total, 321 articles related to DUBs and immunotherapy were retrieved. The number of publications increased markedly since 2020. China had the highest number of publications, while the United States exerted the most influence in this field. Zhang Jinfang was the most influential author in this field. Zhejiang University was the institution with the highest number of publications. Nature was the most cited journal (807 total citations). Keyword analysis revealed that the primary research hotspots were expression, immunotherapy, ubiquitination, degradation, and cancer. This bibliometric analysis revealed the research trends and emerging frontiers in DUBs and immunotherapy, offering novel strategies for the application of DUBs in immunotherapy.

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Deubiquitinases; deubiquitination; immunotherapy; tumor immune microenvironment; bibliometric analysis

Introduction

The ubiquitin-proteasome system (USP) serves as a fundamental regulatory mechanism for intracellular protein turnover, regulating both protein degradation and transport. This pathway comprises ubiquitin (Ub), ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), ubiquitin ligase (E3), and the proteasome.[1] Ubiquitin, which is a small protein with 76 amino acids, is primarily utilized to label proteins for degradation.[2] The E1 enzyme activates ubiquitin to form ubiquitin adenylate. Meanwhile, the E2 enzyme transfers the activated ubiquitin to the E3 enzyme, which recognizes and binds the target protein for its ubiquitination.[3] In addition to facilitating protein degradation, ubiquitination modulates the activity and localization of proteins, maintaining intracellular protein homeostasis.[4]

Deubiquitinating enzymes (DUBs) are critical regulators of the USP that reverse ubiquitination by removing ubiquitin moieties from target proteins.[5] The balance between ubiquitination and deubiquitination is crucial for cellular processes such as cell cycle progression, DNA repair, transcriptional regulation, and immune signaling.[6] Recent studies have reported that DUBs are involved in shaping the tumor immune microenvironment (TIME) and regulating key immune processes, such as antigen presentation, immune checkpoint pathways, and inflammatory responses.[7] Additionally, DUBs influence T-cell activation, macrophage polarization, and regulatory T-cell function, contributing to immune suppression or activation. Thus, targeting specific DUBs is a potential strategy to enhance anti-tumor immune response and improve immunotherapy efficacy.

Recent studies have identified specific DUBs that regulate immune responses through distinct molecular mechanisms. For example, USP7, CYLD, and A20 regulate T-cell activation, inflammation, and tumor immune escape through the modulation of NF-κB signaling and antigen presentation.[8] Meanwhile,

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USP22 stabilizes programmed cell death ligand 1 (PD-L1) to promote tumor immune evasion (Yanyan.[9] PD-L1, which is expressed on the tumor cell surface, binds to programmed cell death protein 1 (PD-1) on T cells, leading to T-cell exhaustion and immune suppression and the evasion of immune surveillance by tumor cells. USP4 modulates tumor growth factor TGF-β signaling to regulate immunosuppressive pathways in the tumor microenvironment.[10] Moreover, studies suggest that targeting USP15 could provide a novel therapeutic strategy for autoimmune diseases by inhibiting the excessive production of interferons and pro-inflammatory cytokines.[11] Together, these findings demonstrate the diverse roles of DUBs in shaping immune responses, revealing their potential as targets to enhance the efficacy of immunotherapies.

However, a comprehensive analysis of research trends, key contributors, and emerging hotspots in this field has not been performed. Traditional articles provide valuable insights but are often limited by their qualitative nature and inherent subjectivity. In contrast, bibliometric analysis offers a robust, data-driven approach to systematically map the research landscape, identify influential studies, and track evolving trends at the intersection of DUBs and immunotherapy.[12] To the best of our knowledge, no bibliometric studies have systematically explored the relationship between DUBs and immunotherapy. This study performed bibliometric analysis to systematically evaluate research on DUBs and immunotherapy in the last decade. This approach provided a comprehensive overview of the field and enhanced our understanding of the role of DUBs in immunotherapy, offering valuable insights for future research directions and therapeutic strategies.

Materials and methods

Search strategy

Web of Science, an academic literature database platform offered by Clarivate Analytics, Inc., encompasses information across the hard sciences, social sciences, arts, and humanities. This database, which is globally recognized as an independent citation database that offers citation indexing, bibliometric analysis, and other functionalities, is widely used in academic research and scientific evaluation.[13] The literature for this study was sourced from the Web of Science Core Collection database. The search formula was as follows: TS = (("USP" OR "DUBs" OR "Deubiquitinase" OR "Deubiquitinases" OR "Ubiquitination" OR "Deubiquitination" OR "Ubiquitin-Proteasome System") AND ("Immunotherapy")). The search was conducted on May 3, 2024, to ensure the timeliness of the data. The search period was defined as April 30, 2014, to April 30, 2024; In total, 326 articles were retrieved.

Data filtering processing

During the literature screening process, we followed the criteria outlined below: only studies focusing on DUBs and immunotherapy were included, the studies had to be published

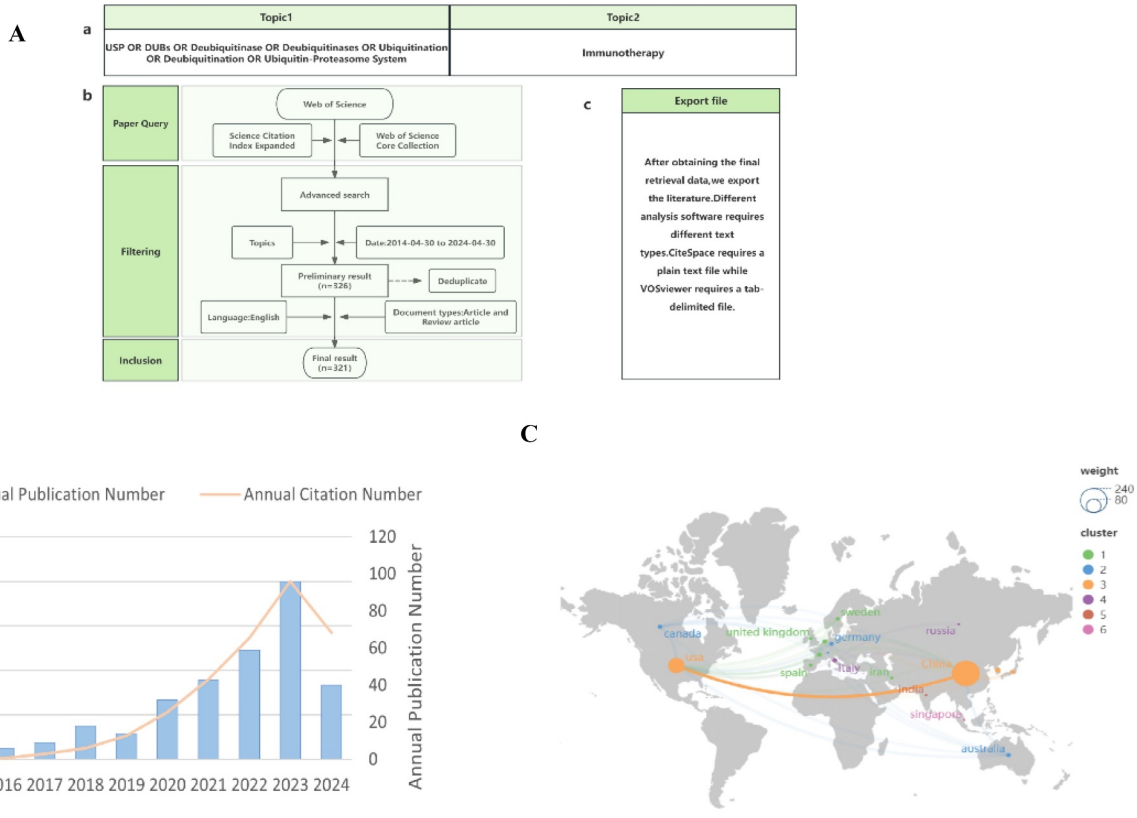


Figure 1. A: (a) (b) Search strategy and flowchart for literature screening. (c) Export format types. B: Overall trends in publications and citations from 2014 to 2024. The left vertical axis shows the total number of citations per year, while the right vertical axis indicates the annual number of publications. C: Vosviewer and SCImago draw the country collaboration map.

in English, and the article types were restricted to research articles and reviews. Figure 1 illustrates the specific process used to search for the articles. In total, 321 publications were included in the bibliometric analysis, comprising 254 research articles and 67 reviews. CiteSpace exports a plain text file, while VOSviewer exports a tab-separated file that includes details, such as the title, author, keywords, institution, country, journal of publication, references, and citation counts.

Bibliometric data analysis

The exported data were imported into CiteSpace (6.3.R1), VOSviewer (1.6.18), Microsoft Office Excel (2021), and R software (4.4.0) using the Bibliometrix package for bibliometric analysis.

CiteSpace is an analytical software that integrates scientific analysis and visualization for the processing and display of bibliometric data.[14] This study used CiteSpace to visualize research hotspots related to DUBs and immunotherapy, forecast emerging research frontiers, and analyze keyword co-occurrence and keyword citation bursts. The time slices were set from April 2014 to April 2024, with each slice representing one year. Text processing was conducted using "Title," "Abstract," "Author Keywords," and "Keyword Plus." The node type and link strength were set to default values. For node filtering, the g-index was used with *K* set to 15.

VOSviewer efficiently handles large-scale data, visualizing citation and collaborative relationships through network diagrams comprising nodes and connections.[15] Each node represents a document, author, organization, or keyword with the node size corresponding to its frequency. The connecting lines represent the relationships between nodes with line thickness indicating the strength of these connections. Different colors are used to denote various research areas. This study used VOSviewer to analyze research institutions, reference co-citation, journal co-citation, and keyword co-occurrence.

The Bibliometrix package in R was used to extract and quantify the annual publication output and citation trends in this field. The extracted time-series data were further processed in Microsoft Office Excel (2021) to generate visual representations of publication trends, providing a clear and intuitive depiction of the research trajectory in the last decade.

Results

Analysis of publication volume

Based on the search criteria, this study identified 321 publications related to DUBs and immunotherapy published in the last 10 years. The annual publication count serves as a crucial indicator of the research field's pace and emerging trends.[16] The research can be categorized into the following three stages based on the number of publications: the "initial stage," the "exponential growth stage," and the "mature growth stage." From 2014 to 2017, the number of published articles remained relatively stable. During this period, research on deubiquitinating enzymes and immunotherapy was in its nascent stage, beginning to attract attention. From 2017 to 2019, a surge in publications occurred as researchers delved deeply into the field. Despite a slight decline in 2019, publication numbers subsequently increased rapidly. From 2020 to 2023, the research field experienced explosive growth, culminating in 2023 with over three times the number of publications compared to the initial phase. The number of citations has been increasing, particularly in 2023, which saw a peak in both the volume of publications and citations (Figure 1(b)). During this period, research hotspots and cutting-edge topics related to DUBs and immunotherapy piqued the interest of the scientific community, attracting numerous researchers and yielding novel findings. Based on current trends, the number of publications is expected to increase in this research area.

Analysis of interstate relations

VOSviewer and SCImago were used to generate a map of inter-country cooperation relationships (Figure 1(c)). Each line on the map represents the cooperation relationship between countries, with the line thickness indicating the frequency of collaboration. China and the United States had the closest cooperation relationship. As shown in Table 1, China, the United States, South Korea, Italy, and France were the top five ranked countries according to the number of publications. Among these, China was ranked first with a total of 251 publications. "Centrality" is a metric commonly used to evaluate the importance and influence of a node within a network.[17] Although China ranked first in terms of the number of publications, the United States exhibited the highest degree of centrality. These findings indicate that although China publishes the highest number of research papers and is involved in numerous research projects within the field, the United States plays a pivotal role in bridging gaps in international research collaborations. The United States exhibited a strong cross-disciplinary and cross-border influence, which effectively facilitates linkages and collaborations between diverse research groups.

Analysis of author and research institutions

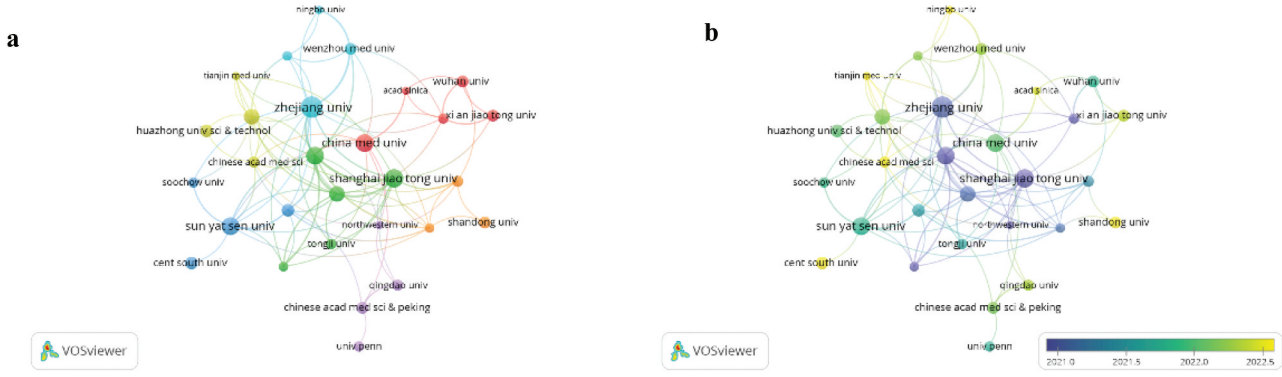
In the bibliometric analysis of author influence in the field of DUBs and immunotherapy, citation count is one of the key indicators of academic contribution. Analysis using VOSviewer revealed that Zhang Jinfang was the most influential author in this field (743 citations), followed by Wei Wenyi (701 citations) and Sun Shaocong (340 citations) (Table 2). Studies by Zhang Jinfang and Wei Wenyi had the most significant impact on the field of DUBs and immunotherapy research. The high citation counts of studies by these authors reflect their substantial academic contribution and standing in the field.

Table 1. Top 5 countries with the highest output in DUBs and immunotherapy research.

Rank	Country	Count	Centrality
1	China	251	0.28
2	USA	84	0.41
3	South Korea	8	0.00
4	Italy	7	0.18
5	France	7	0.07

Table 2. The top 5 most influential authors in DUBs and immunotherapy.

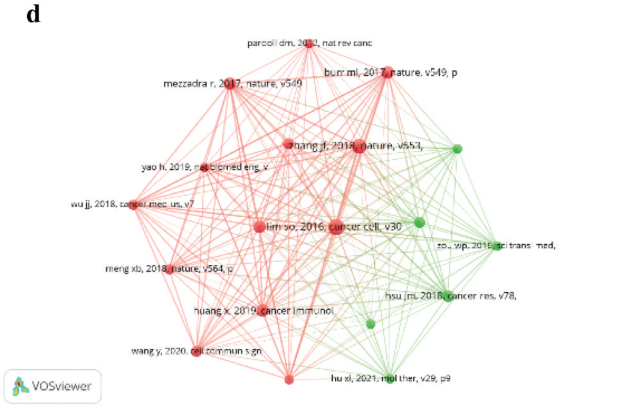
Rank	Author	Citations	Documents	H
1	Zhang jinfang	743	5	36
2	Wei wenyi	701	4	73
3	Sun shaocong	340	6	66
4	Liu lu	193	4	5
5	Bai xueli	108	4	43



c

Top 10 Institutions with the Strongest Citation Bursts

Institutions	Year	Strength	Begin	End	2014 - 2024
University of Texas System	2015	1.89	2015	2019	
UTMD Anderson Cancer Center	2015	1.73	2015	2017	
Consejo Superior de Investigaciones Cientificas (CSIC)	2015	1.53	2015	2018	
Center for Excellence in Molecular Cell Science	2016	1.67	2016	2020	
University of Chinese Academy of Sciences	2018	1.39	2018	2020	
Harvard University	2020	1.96	2020	2022	
Harvard Medical School	2020	1.63	2020	2022	
Tongji University	2020	1.49	2020	2021	
Huazhong University of Science & Technology	2020	1.32	2020	2021	
Peking Union Medical College	2022	1.31	2022	2024	



e

Top 15 References with the Strongest Citation Bursts

References	Year	Strength	Begin	End	2014 - 2024
Akbay EA, 2013, CANCER DISCOV, V3, P1355, DOI 10.1158/2159-8290.CD-13-0310, DOI	2013	1.25	2016	2018	
Lim SO, 2016, CANCER CELL, V30, P925, DOI 10.1016/j.ccell.2016.10.010, DOI	2016	7.37	2018	2021	
Burr ML, 2017, NATURE, V549, P101, DOI 10.1038/nature23643, DOI	2017	4.33	2018	2022	
Li CW, 2018, CANCER CELL, V33, P187, DOI 10.1016/j.ccell.2018.01.009, DOI	2018	2.29	2019	2020	
Wei SC, 2018, CANCER DISCOV, V8, P1069, DOI 10.1158/2159-8290.CD-18-0367, DOI	2018	2.16	2019	2021	
Li CW, 2016, NAT COMMUN, V7, P0, DOI 10.1038/ncomms12632, DOI	2016	6	2020	2021	
Chen DS, 2017, NATURE, V541, P321, DOI 10.1038/nature21349, DOI	2017	2	2020	2021	
Hu HB, 2016, CELL RES, V26, P457, DOI 10.1038/cr.2016.40, DOI	2016	2	2020	2021	
Mezzadra R, 2017, NATURE, V549, P106, DOI 10.1038/nature23669, DOI	2017	4.64	2021	2022	
Chen G, 2018, NATURE, V560, P382, DOI 10.1038/s41586-018-0392-8, DOI	2018	2.22	2021	2022	
Horita H, 2017, NEOPLASIA, V19, P346, DOI 10.1016/j.neo.2017.02.006, DOI	2017	1.9	2021	2022	
Schauer NJ, 2020, J MED CHEM, V63, P2731, DOI 10.1021/acs.jmedchem.9b01138, DOI	2020	1.9	2021	2022	
Sun C, 2018, IMMUNITY, V48, P434, DOI 10.1016/j.immuni.2018.03.014, DOI	2018	1.09	2021	2022	
Li JY, 2020, CANCER IMMUNOL RES, V8, P282, DOI 10.1158/2326-6066.CIR-19-0661, DOI	2020	2.32	2022	2024	
Hegde PS, 2020, IMMUNITY, V52, P17, DOI 10.1016/j.immuni.2019.12.011, DOI	2020	2.06	2022	2024	

Figure 2. Analysis of research institutions (a): Visualization of research institutions (b): Visualization of overlays over time in research institutions (c): top 10 institutions with the strongest citation bursts (d): the visualization of co-cited references (e): top 15 references with the strongest citation bursts.

Based on VOSviewer analysis of research institutions (Figure 2(a)), a criterion of at least five publications per institution was established. In total, 530 institutions satisfied this criterion. The institutions with the highest number of publications were Zhejiang University, Shanghai Jiao Tong University, the Chinese Academy of Sciences, Sun Yat-sen University, and China Medical University. The substantial output of these institutions in the field of DUBs and immunotherapy research highlights their scientific strength and research focus, contributing significantly to advancements in this area. A superimposed visualization of institutional contributions over time is presented in Figure 2(b). Recently, Shandong University, Tianjin University, and Central South University have initiated research on DUBs and

immunotherapy. This trend indicates the growing importance and appeal of this research area, as well as the diversification of research perspectives and methodologies, reflecting the strengthening of scientific research across various regions of China. As shown in Figure 2(c), studies from the University of Texas, the University of Texas M. D. Anderson Cancer Center, and the Supreme Council for Scientific Research (CSIC) were the most frequently cited. Most of these institutions are based in Europe and the United States, while most publications are from China. In contrast, European and American institutions excel in quality and impact, highlighting the complementary nature and collaborative efforts of different regions in producing research output.

Analysis of co-cited references and citation bursts

In the last 10 years 18,272 co-citations related to research on DUBs and immunotherapy were identified. This study selected studies with a co-citation count of > 20 for mapping. As shown in Figure 2(d), 19 studies satisfied this criterion. Lim et al.,[18], Zhang[19], Burr[20], and Mezzadra[21] exhibited a close co-citation relationship. The top 15 citation bursts are highlighted in Figure 2(f). The strongest citation burst occurred in 2018 for the article titled "Deubiquitination and Stabilization of PD-L1 by CSN5" (burst strength = 7.37). The article, which was published by Seung-Oe Lim in the *journal Cancer Cell*, demonstrated that CSN5 can enhance the effectiveness of immunotherapy by decreasing the ubiquitination of PD-L1 and stabilizing its protein structure. In particular, CSN5 inhibited the ubiquitination of PD-L1 and enhanced its stability on the surface of tumor cells. This may result in the overexpression of PD-L1, impairing immune cell activation and hindering tumor immune progression. Additionally, CSN5 intervention influenced the effectiveness of anti-CTLA4 immunotherapy by enhancing the function of anti-tumor T cells and suppressing tumor growth. This article has been extensively cited due to its significance and impact, revealing the crucial role of CSN5 in regulating PD-L1 stability and its implications for immunotherapy.[18] Thus, DUBs may play a critical role in tumor immunotherapy response by modulating the ubiquitination status of PD-L1. This modulation potentially impacts the effectiveness of immune checkpoint inhibitors and influences the prognosis of patients with cancer. This article is also among the most frequently cited articles overall.

Analysis of journal and co-cited journal

Studies related to DUBs and immunotherapy were published in 158 journals and 1,923 co-cited journals. The journal with the highest number of articles was *Nature Communications* (14 articles), followed by *Journal for ImmunoTherapy of Cancer* (13 articles) and *Frontiers in Immunology* (12 articles). Table 3 lists the top 10 co-cited journals, among which three have been cited more than 500 times each. *Nature* was the most cited journal (total citations = 807), followed by *Nature Communications* (total citations = 577) and *Cancer Research* (total citations = 522). The journals were clustered and analyzed using VOSviewer. These journals can be broadly categorized into three groups (Figure 3(a)).

Table 3. Top 10 co-cited journal related to DUBs and immunotherapy.

Sources	Total citations	Centrality	IF
NATURE	807	0.01	50.5
NAT COMMUN	577	0.06	14.7
CANCER RES	522	0.06	12.5
CELL	490	0.02	45.5
P NATL ACAD SCI USA	475	0.02	9.4
J BIOL CHEM	419	0.03	4.0
SCIENCE	384	0.03	44.7
IMMUNITY	342	0.01	25.5
J IMMUNOL	332	0.04	3.6
MOL CELL	322	0.03	14.5

The blue cluster predominantly comprised *Nature*, *The Journal of Biological Chemistry*, *Cell*, *PLoS ONE*, *Proceedings of the National Academy of Sciences USA*, and *Molecular Cell*. These high-impact journals publish research that garners significant attention and discussion within the academic community. Additionally, these journals often encompass various subject areas, such as cell biology and molecular biology, and publish studies with high citation frequency and impact factors.

The red cluster primarily comprised *Cancer Research*, *New England Journal of Medicine*, *Clinical Cancer Research, Cancer Cell*, *Journal of Clinical Oncology*, and *Blood*. These journals publish specialized studies in particular research areas, such as cancer research and clinical medicine. Additionally, these journals typically publish research findings that hold substantial academic significance and impact within their respective fields, playing a crucial role in advancing progress in these areas.

The green cluster primarily comprised *Nature Communications*, *Immunity*, *Journal of Immunology*, *Journal of Experimental Medicine*, *Nature Reviews Immunology*, *Nature Medicine*, and *Frontiers in Immunology*. These journals specifically publish studies in the fields of immunology and immunological studies. Immunology explores the structure and function of the immune system, as well as its role in disease development and treatment. The findings published in these journals within this field exhibit significant impact and citation rates.

Analysis of research hotspots and frontiers

Keywords represent the core concepts of the literature's subject matter, significant terms within the field, or essential elements of the research. Analysis of keywords can reveal research hotspots and development trends, aiding researchers to understand the dynamics of the field.[22] As shown in Figure 3(b-c), CiteSpace and VOSviewer analysis revealed that the terms "expression," "immunotherapy," "ubiquitination," "degradation," and "cancer" were the most frequently reported keywords. VOSviewer keyword clustering analysis (Figure 3(c)) revealed that "immunotherapy," "expression," and "ubiquitination" were among the keywords that occurred at least 10 times. "cancer" and "PD-L1" were also

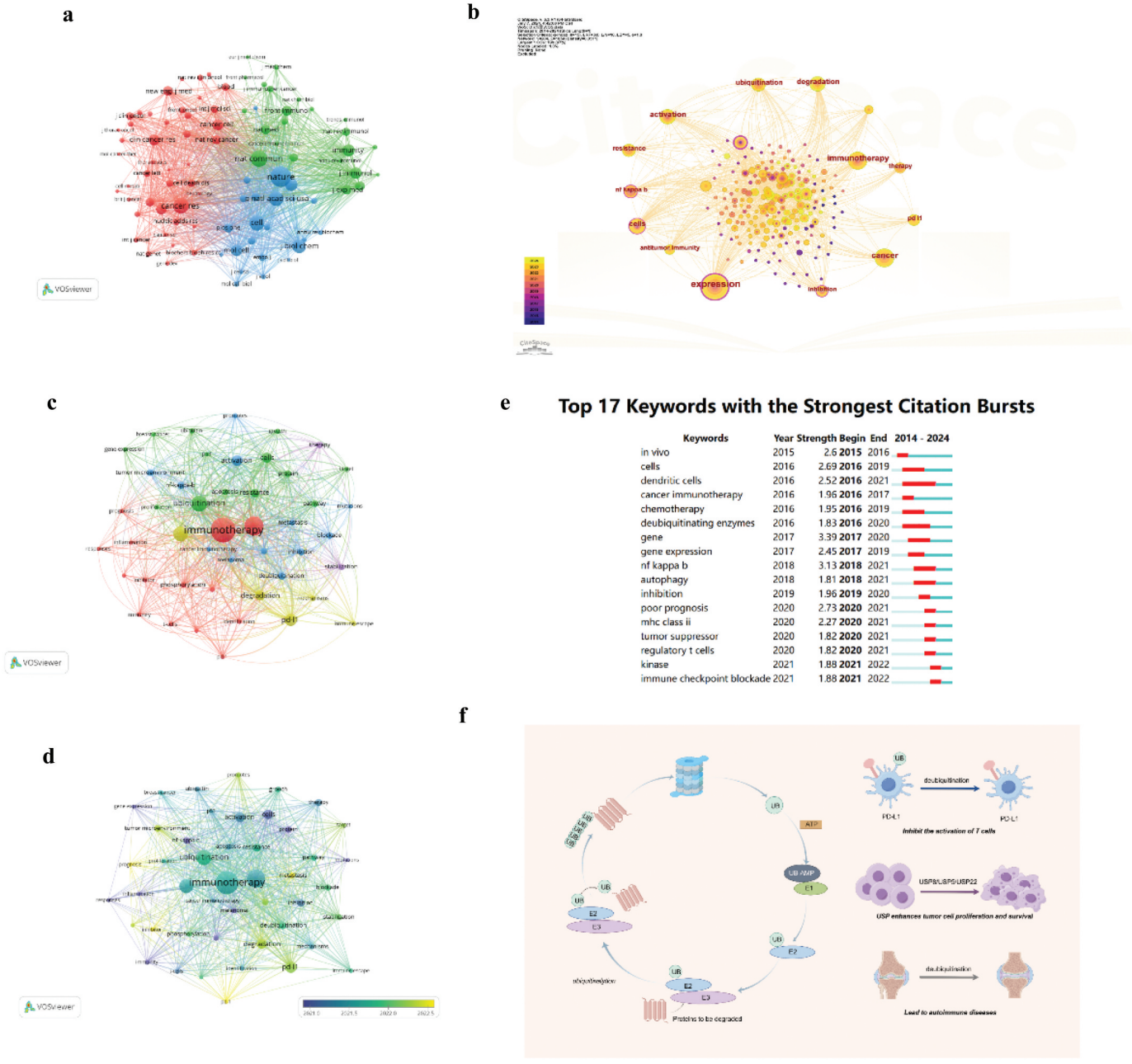


Figure 3. (a): Journal clustering analysis. (b): CiteSpace keyword Co-occurrence map. (c): VOSviewer keyword clustering. (d): Keyword time trend graph. (e): Keywords with the strongest citation bursts. (f): Mechanisms of deubiquitinating enzymes and their application in immunotherapy.

frequently reported keywords, suggesting that these topics are key areas of interest and research hotspots in the field. As shown in Figure 3(d), "PD-1," "prognosis," "metastasis," and "inhibitor" are the current research hotspots. Figure 3(e) illustrates the 17 keywords with the strongest citation bursts. The keyword "Dendritic cells" had the longest citation burst duration, extending from 2016 to 2021. This suggests the sustained significance and ongoing research enthusiasm surrounding dendritic cells in this field of study. The keyword "deubiquitinating enzymes" had the second longest citation burst duration, with a notable surge from 2016 to 2020, indicating a significant impact of DUBs on immunotherapy research. Recently, the number of studies on tumor suppressors, regulatory T cells, kinases, and immune checkpoint blockade has markedly increased. This trend indicates a growing interest among researchers in applying DUB inhibitors to immunotherapy.

Discussion

General information

This study performed bibliometric analysis to systematically elucidate the research trends of DUBs in immunotherapy from 2014 to 2024. Since 2018, the number of publications and citations has markedly increased in this field, reflecting the critical biological role of DUBs in immunotherapy and highlighting the growing research interest in this area. Numerous studies have focused on

targeting DUBs to enhance the function of immune cells, such as T cells and dendritic cells, and consequently improve the efficacy of anti-tumor immune responses.

An analysis of international collaborations revealed that China and the United States were among the countries with the highest publication volume, reflecting the growing interest in examining the role of DUBs in immunotherapy in these countries. However, the research approaches in China and the United States varied. The United States has facilitated the clinical translation of DUB inhibitors through extensive international collaborations, such as partnerships with institutions in Germany and Australia, integrating interdisciplinary resources. For example, the clinical trial of the USP7 inhibitor at MD Anderson Cancer Center (NCT04504096) relied on international cooperation for preclinical validation, demonstrating the efficiency of multi-center collaboration.[23] In contrast, research in China primarily focuses on the exploration of fundamental mechanisms. For example, the study conducted by the Tongji Medical College team demonstrated that USP7 inhibitors can enhance the expression of PD-L1 in tumors.[24] This finding offers new insights into targeted therapy. However, this approach lacks international collaboration, limiting the global impact of these research outcomes.

The most frequently co-cited article (*Deubiquitination and Stabilization of PD-L1 by CSN5*, published in *Cancer Cell*) elucidates the critical role of DUBs in promoting tumor immune evasion through PD-L1 stabilization. This study marks a pivotal shift in DUB research from fundamental mechanistic investigations to therapeutic target exploration.[18] The emergence timeline of the keyword "immune checkpoint blockade" closely aligns with the surge in preclinical combination therapy studies. This trend reveals the guiding role of fundamental research in clinical translation and highlights the necessity for further exploration of the practical applications of DUBs in immunotherapy.

Research hotspots and frontiers

Analysis of burst keywords, high-frequency keywords, and keyword clustering revealed that the primary research hotspots in the study of DUBs and immunotherapy are centered on immunotherapy, DUBs, and the TIME.

Immunotherapy

The concept of immunotherapy was initially developed by German physicians Wilhelm Busch and Paul Ehrlich during the late 19th century. Paul Ehrlich's concept of utilizing serotherapy and immunotherapy to combat disease is considered a major early contribution to immunomodulatory therapy. Additionally, the concept of immunotherapy was explored by the German physician Otto Wolff in his 1886 paper titled "The Serum Therapy in the Diphtheria Morbid Process."[25] These early studies established the foundation for the development of immunotherapy and have significant implications for contemporary research in this field. Currently, immunotherapy, an emerging therapeutic modality, has achieved substantial advancements in the treatment of tumors.

The mechanisms of immunotherapy in tumor treatment involve two primary aspects:

First, the immune system is activated, enhancing the body's ability to recognize and target tumor cells. Second, a mechanism is activated to prevent tumor cells from evading immune responses.[26] The primary strategies for activating the immune system involve enhancing the function of immune cells, such as T cells and natural killer (NK) cells, to improve their ability to recognize and target tumor cells.[27,28] The immune escape mechanism of tumor cells is inhibited using immune checkpoint inhibitors, such as CTLA-4 and PD-1 inhibitors, preventing the tumor cells from evading T-cell-mediated immune response. Additionally, strategies, such as tumor vaccines and CAR-T-cell therapies are utilized to enhance the immune system's ability to attack, as well as to restore the activity of immune cells, enabling them to target tumor cells.[29] These mechanisms synergistically function to inhibit the immune escape capabilities of tumor cells and enhance the immune system's capacity to recognize and target tumor cells.

DUBs and the TIME

The roles of DUBs in various pathophysiological processes have been extensively studied. In addition to tumor immune escape, DUBs are associated with the TIME, regulating the immune response. In the tumor microenvironment, the anti-tumor immune response is crucial for tumor suppression. USP is considered a novel immunotherapeutic target for cancer.[30,31]

To further illustrate this concept, Xing Huang et al. demonstrated that USP22 inhibitors suppress hepatocellular carcinoma growth through an immune mechanism. These inhibitors directly bind to the C-terminus of CD274, induce ubiquitination, upregulate CD274-targeted immunotherapeutic response, and enhance anti-tumor efficacy.[32] Additionally, Ren et al. demonstrated that the pharmacological targeting of OTUB2 promotes PD-L1 degradation, increasing the sensitivity of tumor cells to T cells. This finding indicates that OTUB2 is a viable immunotherapeutic target for cancer, providing a foundation for establishing DUB-targeted immunotherapy.[33]

DUBs have not only been confirmed to play an important regulatory role in cancer immunotherapy, but also been found to be closely related to the pathological mechanism of autoimmune diseases. Niraj Parihar et al. reported that DUBs and E3 ligases specifically cleave target proteins and regulate their activity and expression. Additionally, DUBs and E3 ligases modulate the progression of autoimmune diseases through a reversible process involving ubiquitination and deubiquitination.[34] As a leading area in medical research, the integration of modern technology with the study of DUBs, alongside the application of targeted therapies to address immune system dysregulation, not only advances the treatment of TIME but also significantly contributes to the management of autoimmune diseases.

Future directions

This study used a bibliometric analysis to explore the mechanisms of DUBs (Figure 3(f)) and their applications in immunotherapy (Table 4), revealing significant research potential in areas, such as drug development, tumor biomarkers, the TIME, and autoimmune diseases.

Table 4. Application and research of DUBS and immunotherapy.

Diseases	Mechanisms and research	DUBs	References
lung cancer	Inhibiting USP7 boosts PD-L1 expression, synergizing with PD-1 for anti-tumor effects.	USP7	10 .7150/thno.47137
lung cancer	USP12 downregulation leads to excessive activation of NF-κB, inhibits T cell activation, and promotes tumor growth.	USP12	10 .1038/s41467-021 -25,032-5
liver cancer	PRDM1 boosts USP22 transcription, reducing SPI1 degradation and enhancing PD-L1 transcription.	USP22	10 .1038/s41467-022 -35,469-x
liver cancer	USP32 is linked to cancer signaling and cellular behavior pathways, significantly associated with immune cell infiltration.	USP32	10 .1186/s12885-023 -11,617-4
Triple negative breast cancer	USP15 suppresses PD-L1 transcription, increasing CD8 T cell infiltration and enhancing TNBC immunotherapy effectiveness.	USP15	10 .1016/j. canlet.2024.216764
colorectal cancer	Knocking down USP14 decreases IDO1 expression and enhances PD-1 inhibition.	USP14	10 .1038/s41467-022 -33,285-x
colorectal cancer	Upregulating OTUD1 stabilizes FGL1 and inhibits tumor progression.	OTUD1	10 .1038/s41467-022 -33,285-x
Non small cell lung cancer	USP5 interacts directly with PD-L1, enhancing its protein stability.	USP5	10 .1038/s41419-021 -04,356-6
gastric cancer	USP7 inhibitors reduce PD-L1 expression and enhance anti-tumor immunity.	USP7	10 .1016/j. apsb.2020.11.005
Pancreatic cancer	Combined application of USP8 inhibitors with anti-PD-L1 therapy suppresses pancreatic tumor growth.	USP8	10 .1038/s41418-022 -01,102-z
Breast cancer	USP22 inhibits CD73 ubiquitination, reducing tumor growth and metastasis.	USP22	PMC9827093
	USP5 regulates PD-1 protein deubiquitination to impact its function and efficacy in tumor immunotherapy.	USP5	10 .1038/s41467-023 -38,605-3
	Deubiquitinase ATXN3 as a positive regulator of PD-L1 promotes immune evasion in tumor cells.	ATXN3	10 .1172/JCI167728
	Inhibiting USP18 may lead to expansion of interferon-induced gene pool, enhancing pyroptosis in cancer cells.	USP18	10 .1038/s41467-022 -35,348-5
	USP44 stabilizes FOXP3, aiding Treg cells in dampening excessive immune responses during inflammation to maintain immune balance.	USP44	10 .15252/ embr.202050308
	USP22 regulates PD-L1 stability via deubiquitination and controls PD-L1 levels through the USP22-CSN5-PD-L1 axis.	USP22	10 .1186/s12964-020 -00,612-y
	OTUB1 interacts with PL-L1's K48 polyubiquitin chain, preventing its degradation and reducing its interaction with tumor cells.	OTUB1	10 .1038/s41418-020 -00,700-z
Autoimmune diseases	Abnormal NF-κB activation in inflammation and autoimmune diseases is linked to A20 deubiquitinase defects.	A20	10 .3109/ 08916934.2014.900756
Autoimmune diseases	OTUD1 maintains immune homeostasis; loss-of-function mutations enhance immune responses and correlate with autoimmunity.	OTUD1	10 .1016/j. jaut.2018.07.019

Drug development

DUBs promote PD-1 post-transcriptional modification (PTM) to regulate the stability of PD-L1.[35] DUBs, which modulate the deubiquitination of PD-L1, enhance the anti-tumor efficacy of immune cells. PTMs targeting PD-L1 are expected to be a key focus in drug development. Previous studies have reported that natural food compounds, small molecule inhibitors, and monoclonal antibodies that target the PD-L1 PTM exhibit promising potential for cancer therapy. Thus, agents targeting the PD-L1 PTM regulatory signaling pathway are potential novel immunotherapy drugs.[35,36] Future research must focus on enhancing the selectivity and efficacy of DUB inhibitors, assessing their safety and effectiveness in clinical settings, and developing personalized immunotherapy.

Tumor biomarkers

A tumor biomarker is a biological characteristic or molecular indicator used for diagnosing, monitoring, or assessing the prognosis of a tumor throughout its occurrence, development, and treatment.[37] The responses of patients to DUB inhibitors are being assessed in clinical studies.[7] For example, biological samples relevant to the patients' pathophysiological findings were collected and utilized to analyze the levels of biomarkers, including PD-L1 expression and T-cell infiltration, and to perform correlation analysis with treatment outcomes.[38] The biomarkers that can accurately predict a patient's response to immunotherapy can be identified using this approach. The discovery and application of biomarkers will represent a significant research direction in future studies on DUBs and immunotherapy.

TIME

The TIME, a complex ecosystem, plays a critical role in both tumor development and therapy response.[39] DUBs play a crucial role in regulating the TIME. Future studies must focus on reshaping the TIME by modulating DUBs. For example, promoting immune cell infiltration enhances the capacity of T cells and NK cells to recognize and attack tumors, increasing the efficacy of immunotherapy.[40] Enhancing immunotherapy effectiveness by modulating the mechanisms of the TIME lays a practical foundation for future protocols involving DUBs and immunotherapy.

Autoimmune diseases

Autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis, are a group of disorders characterized by aberrant immune responses against the body's own tissues and organs.[41] DUB activity modulation can modulate immune cell

function and the strength of the immune response, alleviating the symptoms of autoimmune diseases. Initial studies should focus on exploring the mechanisms through which DUBs influence different autoimmune diseases, especially through the modulation of autoantigen presentation or autoantibody production.[42] Subsequent studies must focus on the development of inhibitors or enhancers targeting specific DUBs to alleviate aberrant immune responses.[43] The impact of these treatment strategies on patients' quality of life must be evaluated, focusing on mitigating disease symptoms and delaying disease progression. These efforts will drive the development of new and effective treatments for autoimmune diseases, harnessing innovative strategies to overcome therapeutic challenges.

Challenges and limitations

DUBS are crucial for modulating the activity and function of immune cells. The inhibition of DUBs can modulate the magnitude and timing of the immune response, enhancing or suppressing immune responses against pathogens or tumor cells. However, ubiquitinase family members are diverse with complex functions and exhibit varying functions in different cells and tissues. The identification of specific DUBs targets for application in targeted immunotherapy is challenging. Furthermore, inhibiting ubiquitinating enzymes may adversely affect healthy cells and tissues, leading to the development of immune disorders. Additionally, bibliometric analysis depends on preexisting databases and indexing systems that may have missing or incomplete data. However, this limitation has a minor impact on the results and a negligible effect on the direction of research and emerging trends.

Conclusions

A bibliometric analysis of publication trends indicated that research on DUBs and immunotherapy has entered a phase of rapid development in recent years. Collaborative links between countries are expanding. China is leading in the number of publications, while the United States has the highest level of influence. The current study reveals that leading research topics are focused on DUBs, immunotherapy, and the TIME. Future research and applications should focus on identifying DUBs with enhanced specificity and minimal side effects for application in immunotherapy.

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Author contributions

Xia Chen: Designed the research, conducted data analysis, and wrote the initial draft of the manuscript. Yang Qin: Supervised the research, provided editorial review, and conceptualized the study. Jinfeng Gan: Wrote, reviewed, and edited the manuscript. Tangwen Wei: Conceptualized the study and conducted data analysis. Xinyi Wei: Conducted data analysis and created visualizations. Yaling Xiong: Responsible for data management and validation. Zhichang Zhang: Responsible for writing, reviewing, software analysis, and methodology. Bing Wei: Responsible for writing, peer review, and securing funding.

Data availability statement

All data are available on Web of Science.

References

1. Sun T, Liu Z, Yang Q. The role of ubiquitination and deubiquitination in cancer metabolism. Mol Cancer. 2020;19(1):146. doi: 10.1186/s12943-020-01262-x.
2. Komander D, Rape M. The ubiquitin code. Annu Rev Biochem. 2012;81(1):203–229. doi: 10.1146/annurev-biochem-060310-170328.
3. Mulder MP, Witting K, Berlin I, Pruneda JN, Wu KP, Chang JG, Ovaa H. A cascading activity-based probe sequentially targets E1-E2-E3 ubiquitin enzymes. Nat Chem Biol. 2016;12(7):523–530. doi: 10.1038/nchembio.2084.
4. Pinto-Fernández A, Davis S, Schofield AB, Scott HC, Zhang P, Salah E, Kessler BM. Comprehensive landscape of active deubiquitinating enzymes profiled by advanced chemoproteomics. Front Chem. 2019;7:592. doi: 10.3389/fchem.2019.00592.
5. Wang J, Zhou Q, Ding J, Yin T, Ye P, Zhang Y. The Conceivable Functions of Protein Ubiquitination and Deubiquitination in Reproduction. Front Physiol. 2022;13:886261. doi: 10.3389/fphys.2022.886261.
6. Kitamura H. Ubiquitin-specific proteases (USPs) and metabolic disorders. Int J Mol Sci. 2023;24(4):3219. doi: 10.3390/ijms24043219.
7. Harrigan JA, Jacq X, Martin NM, Jackson SP. Deubiquitylating enzymes and drug discovery: emerging opportunities. Nat Rev Drug Discov. 2018;17(1):57–78. doi: 10.1038/nrd.2017.152.

8. Guo JN, Xia BR, Deng SH, Yang C, Pi YN, Cui BB, Jin WL. Deubiquitinating enzymes orchestrate the cancer stem cell-immunosuppressive niche dialogue: new perspectives and therapeutic potential. Front Cell Dev Biol. 2021;9:680100. doi: 10.3389/fcell.2021.680100.
9. Zhang Y, Huang Y, Yu D, Xu M, Hu H, Zhang Q, Xia J. Demethylzeylasteral induces PD-L1 ubiquitin–proteasome degradation and promotes antitumor immunity via targeting USP22. Acta Pharmaceutica Sin B. 2024;14(10):4312–4328. doi: 10.1016/j.apsb.2024.08.004.
10. Cao WH, Liu XP, Meng SL, Gao YW, Wang Y, Ma ZL, Wang HB, Wang H-B. USP4 promotes invasion of breast cancer cells via relaxin/TGF-β1/Smad2/MMP-9 signal. Eur Rev Med Pharmacol Sci. 2016;20(6):1115–1122.
11. Chou CK, Chang YT, Korinek M, Chen YT, Yang YT, Leu S, Chiu CC. The regulations of deubiquitinase USP15 and its pathophysiological mechanisms in diseases. Int J Mol Sci. 2017;18(3):483. doi: 10.3390/ijms18030483.
12. Aria M, Cuccurullo C. Bibliometrix: an R-tool for comprehensive science mapping analysis. J Informetrics. 2017;11(4):959–975. doi: 10.1016/j.joi.2017.08.007.
13. Liu X, Zhao S, Tan L, Tan Y, Wang Y, Ye Z, Wang G. Frontier and hot topics in electrochemiluminescence sensing technology based on CiteSpace bibliometric analysis. Biosens Bioelectron. 2022;201:113932. doi: 10.1016/j.bios.2021.113932.
14. Zhang S, Li X, Chen Z, Ouyang Y. A bibliometric analysis of the study of urban green spaces and health behaviors. Front Public Health. 2022;10:1005647. doi: 10.3389/fpubh.2022.1005647.
15. van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics. 2010;84(2):523–538. doi: 10.1007/s11192-009-0146-3.
16. Qin Y, Zhang Q, Liu Y. Analysis of knowledge bases and research focuses of cerebral ischemia-reperfusion from the perspective of mapping knowledge domain. Brain Res Bull. 2020;156:15–24. doi: 10.1016/j.brainresbull.2019.12.004.
17. Zhang Y, Chen M, Liu C, Zhang Z, Fu X. A bibliometric analysis of COVID-19 and physical activity. Medicine (Baltimore). 2022;101(39):e30779. doi: 10.1097/md.0000000000030779.
18. Lim SO, Li CW, Xia W, Cha JH, Chan LC, Wu Y, Hung MC. Deubiquitination and stabilization of PD-L1 by CSN5. Cancer Cell. 2016;30(6):925–939. doi: 10.1016/j.ccell.2016.10.010.
19. Zhang J, Bu X, Wang H, Zhu Y, Geng Y, Nihira NT, Tan Y, Ci Y, Wu F, Dai X, et al. Cyclin D–CDK4 kinase destabilizes PD-L1 via cullin 3–SPOP to control cancer immune surveillance. Nature. 2018;553(7686):91–95. doi: 10.1038/nature25015.
20. Burr ML, Sparbier CE, Chan YC, Williamson JC, Woods K, Beavis PA, Lam EYN, Henderson MA, Bell CC, Stolzenburg S, et al. CMTM6 maintains the expression of PD-L1 and regulates anti-tumour immunity. Nature. 2017;549(7670):101–105. doi: 10.1038/nature23643.
21. Mezzadra R, Sun C, Jae LT, Gomez-Eerland R, De Vries E, Wu W, Logtenberg MEW, Slagter M, Rozeman EA, Hofland I, et al. Identification of CMTM6 and CMTM4 as PD-L1 protein regulators. Nature. 2017;549(7670):106–110. doi: 10.1038/nature23669.
22. Xu B, Wang J, Meng X, Bao B. Bibliometrics and visual analysis of adult-onset still disease (1976-2020). Front Public Health. 2022;10:884780. doi: 10.3389/fpubh.2022.884780.
23. Gui Q, Liu C, Du D. Globalization of science and international scientific collaboration: a network perspective. Geoforum. 2019;105:1–12. doi: 10.1016/j.geoforum.2019.06.017.
24. Dai X, Lu L, Deng S, Meng J, Wan C, Huang J, Sun Y, Hu Y, Wu B, Wu G. USP7 targeting modulates anti-tumor immune response by reprogramming tumor-associated macrophages in lung cancer. Theranostics. 2020;10(20):9332–9347. doi: 10.7150/thno.47137.
25. Demikhovskaia EV, Chudnaia LM, Hardy I. Variants in the immune response to revaccination with diphtheria anatoxin in adults. Zh Mikrobiol Epidemiol Immunobiol. 1999;(5):94–98. https://pubmed.ncbi.nlm.nih.gov/10852032/. PMID: 10852032.
26. Velcheti V, Schalper K. Basic overview of current immunotherapy approaches in cancer. Am Soc Clin Oncol Educ Book. 2016;35(36):298–308. doi: 10.1200/edbk_156572.
27. Grossenbacher SK, Aguilar EG, Murphy WJ. Leveraging natural killer cells for cancer immunotherapy. Immunotherapy. 2017;9(6):487–497. doi: 10.2217/imt-2017-0013.
28. Yao H, Xu J. Regulation of cancer immune checkpoint: mono- and poly-ubiquitination: tags for fate. Adv Exp Med Biol. 2020;1248:295–324. doi: 10.1007/978-981-15-3266-5_13.
29. Principe DR, Chiec L, Mohindra NA, Munshi HG. Regulatory T-Cells as an emerging barrier to immune checkpoint inhibition in lung cancer. Front Oncol. 2021;11:684098. doi: 10.3389/fonc.2021.684098.
30. Guo J, Zhao J, Fu W, Xu Q, Huang D. Immune evasion and drug resistance mediated by USP22 in cancer: novel targets and mechanisms. Front Immunol. 2022;13:918314. doi: 10.3389/fimmu.2022.918314.
31. Zhan X, He Q, Sheng J, Jiang X, Lin L, Huang Y, Zhang Y. USP12 positively regulates M-MDSC function to inhibit anti-tumour immunity through deubiquitinating and stabilizing p65. Immunology. 2022;167(4):544–557. doi: 10.1111/imm.13552.
32. Huang X, Zhang Q, Lou Y, Wang J, Zhao X, Wang L, Bai X. USP22 deubiquitinates CD274 to suppress anticancer immunity. Cancer Immunol Res. 2019;7(10):1580–1590. doi: 10.1158/2326-6066.Cir-18-0910.
33. Ren W, Xu Z, Chang Y, Ju F, Wu H, Liang Z, Xia N. Pharmaceutical targeting of OTUB2 sensitizes tumors to cytotoxic T cells via degradation of PD-L1. Nat Commun. 2024;15(1):9. doi: 10.1038/s41467-023-44466-7.
34. Parihar N, Bhatt LK. Deubiquitylating enzymes: potential target in autoimmune diseases. Inflammopharmacology. 2021;29(6):1683–1699. doi: 10.1007/s10787-021-00890-z.
35. Kim SB, Hwang S, Cha JY, Lee HJ. Programmed death ligand 1 regulatory crosstalk with ubiquitination and deubiquitination: implications in cancer immunotherapy. Int J Mol Sci. 2024;25(5):2939. doi: 10.3390/ijms25052939.
36. Lee TA, Tsai EY, Liu SH, Hsu Hung SD, Chang SJ, Chao CH, Li CW. Post-translational modification of PD-1: potential targets for cancer immunotherapy. Cancer Res. 2024;84(6):800–807. doi: 10.1158/0008-5472.Can-23-2664.
37. Shi Y, Yao M, Shen S, Wang L, Yao D. Abnormal expression of Krüppel-like transcription factors and their potential values in lung cancer. Heliyon. 2024;10(7):e28292. doi: 10.1016/j.heliyon.2024.e28292.
38. Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. Lancet Oncol. 2016;17(12):e542–e551. doi: 10.1016/s1470-2045(16)30406-5.
39. Wu C, Tan J, Shen H, Deng C, Kleber C, Osterhoff G, Schopow N. Exploring the relationship between metabolism and immune microenvironment in osteosarcoma based on metabolic pathways. J Biomed Sci. 2024;31(1):4. doi: 10.1186/s12929-024-00999-7.
40. Li J, Yuan S, Norgard RJ, Yan F, Yamazoe T, Blanco A, Stanger BZ. Tumor cell-intrinsic USP22 suppresses antitumor immunity in pancreatic cancer. Cancer Immunol Res. 2020;8(3):282–291. doi: 10.1158/2326-6066.Cir-19-0661.
41. Zhang Z, Jin L, Liu L, Zhou M, Zhang X, Zhang L. The intricate relationship between autoimmunity disease and neutrophils death patterns: a love-hate story. Apoptosis. 2023;28(9–10):1259–1284. doi: 10.1007/s10495-023-01874-w.
42. Evans PC, Smith TS, Lai MJ, Williams MG, Burke DF, Heyninck K, Kilshaw PJ. A novel type of deubiquitinating enzyme. J Biol Chem. 2003;278(25):23180–23186. doi: 10.1074/jbc.M301863200.
43. Clague MJ, Heride C, Urbé S. The demographics of the ubiquitin system. Trends Cell Biol. 2015;25(7):417–426. doi: 10.1016/j.tcb.2015.03.002.