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Review Article

Global trends and mechanistic insights into A20 (TNFAIP3) in autoimmunity and inflammation

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Abstract: As a pivotal checkpoint in immune homeostasis, the ubiquitin-editing enzyme A20 (encoded by TNFAIP3) exerts profound control over inflammatory cascades. Beyond its established roles in autoimmunity and malignancy, A20 has recently emerged as a critical determinant of therapeutic outcomes. Despite a wealth of bench-to-bedside mechanistic data, a high-level synthesis of how this research landscape has evolved over the past two decades remains elusive. To bridge this gap, we conducted a comprehensive bibliometric mapping of 3,926 English-language publications indexed in the Web of Science Core Collection from 2003 to 2025. By integrating VOSviewer, CiteSpace, and Microsoft Excel, we dissected the intellectual architecture of the field, ranging from institutional collaborative networks to shifts in keyword co-occurrence. Our analysis reveals a robust, multi-phase expansion of the A20 knowledge base, with annual outputs peaking at over 350 papers in 2025. This momentum is largely propelled by a Sino-American research axis, with core clusters identified at University of California, San Francisco (UCSF), Ghent University, and the Chinese Academy of Sciences. We further highlight the seminal influence of investigators like Geert van Loo and Ingrid E. Wertz, whose work has redefined A20's multifaceted roles in NF-κB signaling and regulated cell death. Collectively, this study delineates the maturation of A20 from a simple negative regulator to a context-dependent therapeutic target, offering a strategic roadmap for future translational and disease-specific investigations.

Keywords: A20, TNFAIP3, autoimmune diseases, chronic inflammation, NF-κB signaling pathway, bibliometric analysis

Introduction

A20 is an enzyme that is involved at the interface between immune signaling and cellular homeostasis, and is encoded by the Tumor necrosis factor-induced protein 3 (TNFAIP3) gene. A20 does not behave like a simple switch but rather as a smart molecular rheostat, as it possesses two functions namely deubiquitase and E3 ligase to control the inflammatory cascade precisely. By dynamically modulating ubiquitination of key signaling proteins, A20 may effectively inhibit the activity of NF-kappa B and minimize the overproduction of pro-inflammatory cytokines, which is a protective mechanism that is important to end aberrant signals triggered by the tumor necrosis factor (TNF), Toll-like receptors (TLRs), and T-cell receptors (TCRs) [1, 2]. Besides its traditional function in transcription, newer theories have also relocated A20 to the center stage in the regulation of programmed cell death, such as apoptosis [3], necroptosis [4], and pyroptosis [5, 6]. This complex role involves altering inflammasome formation and type 1 interferon reaction [7, 8], thus affirming the position of A20 as the supreme regulator of innate immunity, and cell fate.

The role of clinical necessity in the study of A20 is underlined by the disastrous consequences of its malfunction. During the last twenty years, there has been an accumulation of data connecting *TNFAIP3* abnormalities to a wide range of diseases such as rheumatoid arthritis and systemic lupus erythematosus and

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inflammatory bowel disease and neuroinflammation [9-18]. Perhaps most revealingly, the identification of TNFAIP3 haploinsufficiency, a single gene autoinflammatory disorder underscores the essentiality of this protein in preserving systemic resting [19, 20]. Although narrative reviews have superbly summarized the biochemical detail and clinical correlates of A20 [1, 21-23], these qualitative reports do not always provide the longitudinal and data driven view needed to trace the development of the field on a global scale. Even though there has been an explosion of literature, the intellectual framework of A20 studies along with its network of collaboration and the changing boundaries of its research hot spots can be quantified to a large extent.

Aiming to fill the gap in this sphere of scholarly study, we have performed an extensive bibliometric analysis of 3,926 publications related to A20 registered in the database of Web of Science Core Collection (2003-2025). Through the use of VOSviewer and CiteSpace, we have gone beyond mere citation count to map the complex development paths and institutional collaborations that have defined the field. The present paper is not only not a mere enumeration of what was already done but rather attempts to combine quantitative tendencies with new mechanistic ideas and thus provides clear guidance on how the future of A20 studies will go. Through this structured perspective, we are able to recognize the main influencers and cooperation structures that will probably lead the future generation of translational and illness specific studies.

Methods

Data source and literature retrieval

The raw bibliographic data of this analysis were collected through the Web of Science Core Collection (WoSCC, Clarivate Analytics). On February 28, 2026, a broad topic search was done using an optimized query string to ensure coverage of all the A20 related literature available: TS = (A20) OR (TNFAIP3) OR (tumor necrosis factor alpha-induced protein 3) OR (A20 protein, TNFAIP3) OR (A20 haploinsufficiency) OR (HA20).

The sampling frame has been fixed at January 1, 2003-December 31, 2025 in order to follow the direction of the field through more than twenty years. To ensure the quality of the analyzed intellectual structure we used rigorous inclusion criteria that solely considered original research articles and reviews. All supplementary materials were systematically excluded including meeting abstracts, editorials, or proceedings. After a manual auditing and deduplication process, a total of 3,926 unique records were curated in the final cohort. This selection pipeline contains granular maps which are mapped in the PRISMA-compliant flow diagram (**Figure 1**).

Data preprocessing and export

The complete bibliographic metadata and cited references have been exported out of the WoSCC in plain-text format. In order to keep a high-fidelity dataset, a special preprocessing pipeline was introduced that emphasized validation of metadata and elimination of incorrect entries. This procedure made sure that core variables, namely, titles, keywords, author affiliations, and citation metrics were correctly recorded and used in downstream analysis. The quantitative synthesis of publication trajectories and descriptive statistics were done in Microsoft Excel 2021, whereas the longitudinal development of the intellectual structure of the field was mapped in CiteSpace.

Bibliometric and network analysis tools

Our aim has been to obtain a multifaceted view of the A20 research environment by synthesizing three different analytical systems. Our method was to use VOSviewer (v1.6.18) to construct and depict the social and thematic landscape of the field as well as the collaboration networks (of countries, institutions, and authors), journal co-citations and patterns of keywords co-occurrences. In order to improve the readability of this map, we used the association-strength normalization technique and established a minimum of 5 keyword occurrences as an arbitrary cutoff value that would be used to eliminate noise and focus on the central thematic clusters.

At the same time, CiteSpace (v6.2.R3) was used to be an essential software to detect changes over time and cross-disciplinary connections between knowledge. To locate major spikes in the citation behavior, we applied

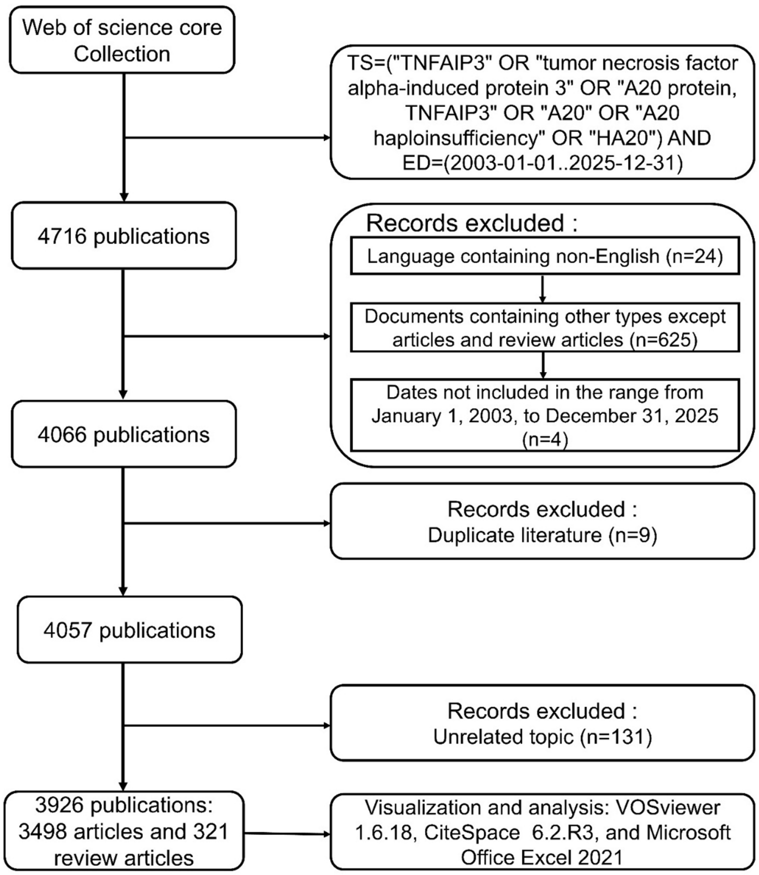


Figure 1. Flow chart for data collection of TNFAIP3-related publications. The schematic diagram illustrates the process of data scraping and filtering. In the data collection step, TNFAIP3/A20-related records were retrieved from the Web of Science Core Collection using a predefined topic search strategy with the time span set from 1 January 2003 to 31 December 2025, restricted to original research articles and review articles written in English, resulting in 3,926 eligible publications.

Kleinberg burst detection algorithm, and then dual-map overlays were created to follow the direction of the knowledge migration in different scientific areas. Our network clustering was assessed using strict metrics based on structure: we made sure that the modularity score was maximal when Q > 0.3 and the mean silhouette score was set so that S > 0.5, which proved the strength of the intellectual clusters that we had defined. Eventually, Microsoft Excel 2021 was utilized to process the raw data and produce detailed graphs of the trends to illustrate each year of publishing dynamics.

Thematic and social topology was determined through visualization of similarities (VOS), a technique that underlies the VOSviewer mapping process, controlling the spatial placement of nodes in accordance with their proximity to linked nodes. In order to divide the A20 research environment into coherent subdomains, we particularly applied the Leiden algorithm, an effective modularity-optimization algorithm that is famous in finding well-structured communities within massive bibliometric networks.

Whereas VOSviewer offered a fixed structural view, CiteSpace was used to observe the development of the field over time. We have cut out unnecessary linkages by using Pathfinder Network Scaling (PFNET) to ensure that we are able to emphasize the most important developmental paths of the citation data. In particular, we took advantage of CiteSpace as a tool for burst detection and used it to find important increases in research momentum because it can effectively transform intricate bibliographic datasets into an understandable trend of new hotspots and changes in intellectual direction regarding A20-related topics.

Inclusion thresholds and methodological validation

In order to define the detail level of our bibliometric maps, we had to specify the particular inclusion limits that are specific to every analytical dimension. In case of institutional co-authorship network, there is a minimum productivity filter (i.e., of the form ≥ 20 publications) to identify the main stakeholders. Likewise, in the case of keyword clustering, the frequency threshold chosen was ≥ 60 in order to distil out the strongest thematic tendencies within the dataset. All the visualized network outcomes were subject to a rigorous manual review to address the shortcomings of automatic clustering and remove any possible misinterpretation bias. The independent qualita-

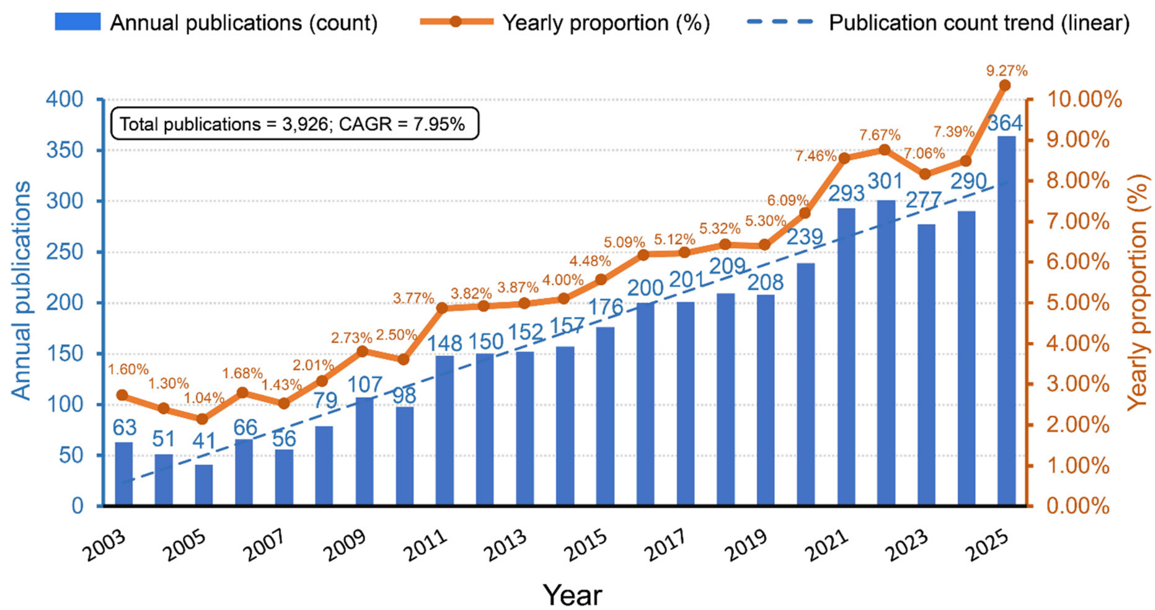


Figure 2. Annual trends of TNFAIP3-related publications. The bar graph shows the number of annual publications on TNFAIP3-related research, while the orange lines represent the proportion of annual publications corresponding to each category. The literature search was performed in the Web of Science Core Collection, focusing on English-language articles and review papers published between January 1, 2003, and December 31, 2025.

tive evaluation of the resulting clusters by two domain experts ensured that the established research hotspots corresponded to existing biological hypotheses, and that the overall accuracy of these findings were maintained.

Ethical considerations

Because this research is purely bibliometric in its character and uses de-identified and publicly available metadata extracted out of scientific databases, it does not qualify as being within the scope of institutional review board (IRB) oversight. Primary data collection involving human or animal subjects was not carried out; therefore, formal ethical approval and informed consent were not required.

Results

Temporal trends in publication output

The historical development of the A20-related literature in the period of 2003-2025 can be described as a developing area of research that is experiencing rapid and enduring growth. Beginning modestly at 63 publications per year in 2003, the yearly scholarship output increased exponentially to 364 articles by 2025, a five-fold rise in production. Shown in **Figure 2**, this longitudinal trend results in a compound annual growth rate (CAGR) of 7.95%, which illustrates a strong interest in the multi-functionality of A20. In 23 years, a total corpus had been achieved of 3,926 papers which is indicative of an evolutionary increase in time, starting with an initial mechanistic discovery and culminating in a more recent and swifter phase of translational exploration.

Contributions by countries and institutions

The geo-economic environment of A20 science can be described as having a clear bipolar focus of scholarship. According to **Table 1** and Supplementary Figure 1A, there has been a solidification of the fact that China and the United States are both the main drivers of production worldwide. China ranks first as the biggest contributor to the quantity with 1,253 papers (31.92%), followed by the US with a close second at 1,155 papers (29.42%). Both of this Sino-US pairings control the discipline and produce more than 60 percent of the overall 3,926 documents. The rest beyond this dual-powers center is underpinned by a strong cadre of wealthy-economy countries such as Germany (298), Japan (252) and England (229). Although their individual contri-

Table 1. Top TNFAIP3 research countries/regions

Rank	Country/Region	Number of Publications	Total Citations	Average Citations per Article	H-index
1	People's Republic of China	1253	25974	20.73	70
2	United States of America	1155	73549	63.68	139
3	Germany	298	16419	55.10	68
4	Japan	252	9096	36.10	54
5	England	229	15101	65.94	63
6	France	149	8449	56.70	48
7	India	145	3731	25.73	36
8	South Korea	138	3791	27.47	35
9	Canada	134	9619	71.78	48
10	Italy	127	5772	45.45	38

Countries/Regions are ranked by the total number of TNFAIP3-related publications in the context of autoimmunity and inflammatory diseases from 1 January 2003 to 31 December 2025. The H-index indicates the citation impact of publications attributed to each country within the retrieved TNFAIP3/A20 dataset. "Average citations per article" was calculated as the total number of citations divided by the number of publications for each country/region.

Table 2. Leading institutions publishing on TNFAIP3 in autoimmune and inflammatory contexts

Rank	Institution Name	Country/ Region	Number of Publications	Total Citations	Average Citations per Article	H-index
1	University of California, San Francisco	USA	85	11942	140.49	52
2	Ghent University	Belgium	82	7630	93.05	52
3	Chinese Academy of Sciences	China	71	2113	29.76	28
4	Harvard University	USA	67	5197	77.57	52
5	Fudan University	China	48	2450	51.04	23
6	Zhejiang University	China	46	2147	46.67	21
7	Shanghai Jiaotong University	China	45	1234	27.42	20
8	University of Tokyo	Japan	42	2123	50.55	26
9	Flanders Institute for Biotechnology VIB	Belgium	41	4304	104.98	53
10	Sun Yat-Sen University	China	40	1869	46.73	19

Institutions are ranked by the number of TNFAIP3-related publications on autoimmunity and inflammatory diseases indexed from January 1, 2003, to December 31, 2025. The H-index indicates the citation impact of publications attributed to each institution within the retrieved TNFAIP3/A20 dataset. "Average citations per article" was calculated as the total number of citations divided by the number of publications for each institution.

butions are less significant than those two giants, these states play an important role as part of the global knowledge network, making great contributions to intellectual growth within the field.

The current A20 research system is enabled by a broad network of 4,466 organizations globally. The intellectual epicenter of the sphere is based on a group of well-established hubs of immunology as listed in **Table 2** and Supplementary Figure 1B. In particular, the University of California, San Francisco (n = 85) and Ghent University (n = 82) continue their role as leaders when it comes to high-impact discoveries. Parallelly, science in China has turned into an influential regional power, where there is a very heavy concentration of high-output institutions. The Chinese Academy of Sciences (n = 71) and a constellation of renowned medical universities, including Fudan University (n = 48), Zhejiang University (n = 46), Shanghai Jiao Tong University (n = 45), and Sun Yat-sen University (n = 40) form the foundation of this activity, and they are all demonstrating a high level of dedication to TNFAIP3 studies, which appears to be both consistent and steady. The productivity trends of the listed leading centers indicate that there is a tactical focus on clarifying the molecular intersection of immunological signaling and inflammatory diseases.

Author productivity and co-citation networks

The social structure of the A20 research community is extremely tight, with a population of 23,173 individuals who contribute to it. By taking a close-up on productivity numbers, it is found that a limited number of high-output investigators who are based in Ghent University and UCSF are driving the momentum of the field, far out of proportion to their share of the overall contribution. These groups are headed by Geert van Loo (52 articles), Rudi Beyaert (51 articles), and Averil Ma (49 articles) who have produced a substantial volume of work over time, which has greatly influenced the current perception of the biology of TNFAIP3 (Supplementary Table 1).

The citation topography, based on a broad base of 91,378 co-cited authors, solidifies more the enduring transatlantic line of power. The fact that this is a U.S.-Belgian dominance can be illustrated on the basis of the top-co-citation ratings, in which nine out of ten most influential scholars have an affiliation either in the USA (six) or Belgium (three), with a growing contribution of China (one). The fundamental foundation of the field is still founded on the original sources such as Ingrid E. Wertz (749 citations), Noula Shembade (663 citations), and Eric G. Lee (641 citations), plus important works published by Lars Vereecke (465 citations) and David L. Boone (419 citations) (Supplementary Table 1). Taken together, these citation trends define a well-established hierarchy of research in which the original discoveries in mechanistic studies remain the catalyst of modern day translational studies.

The social topography of the A20 field, after filtering out the 45 more prolific researchers in the field (10 or more publications), is divided into 17 clusters (**Figure 3A**). The mentioned structural modularity implies a great extent of thematic specialization and the intellectual isolation of the sphere. Examination of these interactive hubs at close quarters indicates that the Belgian research hub built up on the long-term synergy between van Loo and Beyaert has the highest level of internal unity. In contrast, the high-centrality node connecting different segments of domestic research, Ma's laboratory, bridges the North American axis of the collaborative network.

These dynamics of collaboration are reflected in the structure of co-citation of 54 seminal scholars (**Figure 3B**). In this intellectual web, key hubs like Wertz, Shembade and Lee become the major transmitters of information, their large citation frequencies indicating the importance of these nodes as the mechanisms behind synthesis of consensus in the field. Taken together, the bibliometric fingerprints observed in both these papers define the research picture that has traditionally been directed by well-established institutional groupings in Western Europe and North America, and indicates the continued geographical focus on scientific power in the investigation of TNFAIP3.

Journal distribution and co-citation analysis

The citation footprint of A20 studies covers a very wide range of editorial content. As per the summary in Supplementary Table 2, raw output is mostly focused on broad-spectrum and specialized immunology publications with PLoS One (111 articles) and Frontiers in Immunology (83 articles) being the biggest contributors, and then Scientific Reports (70 articles) and the Journal of Biological Chemistry (63 articles).

Nonetheless, by looking at the citation topography more closely it becomes clear that there is a profound disconnect between the sheer number of publications and the long term value of intellectualism. Journals, such as Blood and Proceedings of the National Academy of Sciences (PNAS) have made smaller contributions by way of articles (33 and 27, respectively), but the academic weight they bring is disproportionately large. In particular, Blood stands on the 5th place overall in terms of influence counting 3,781 co-citations regardless the lower volume, and PNAS stands on the 3rd world-wide with 4,182 co-citations (Supplementary Table 2). Such dichotomy highlights an organizational system of knowledge where a chosen subset of multi-disciplinary journals is used as the leading repository of the core discoveries in the area, actively guiding the orientation of all the subsequent A20-related research.

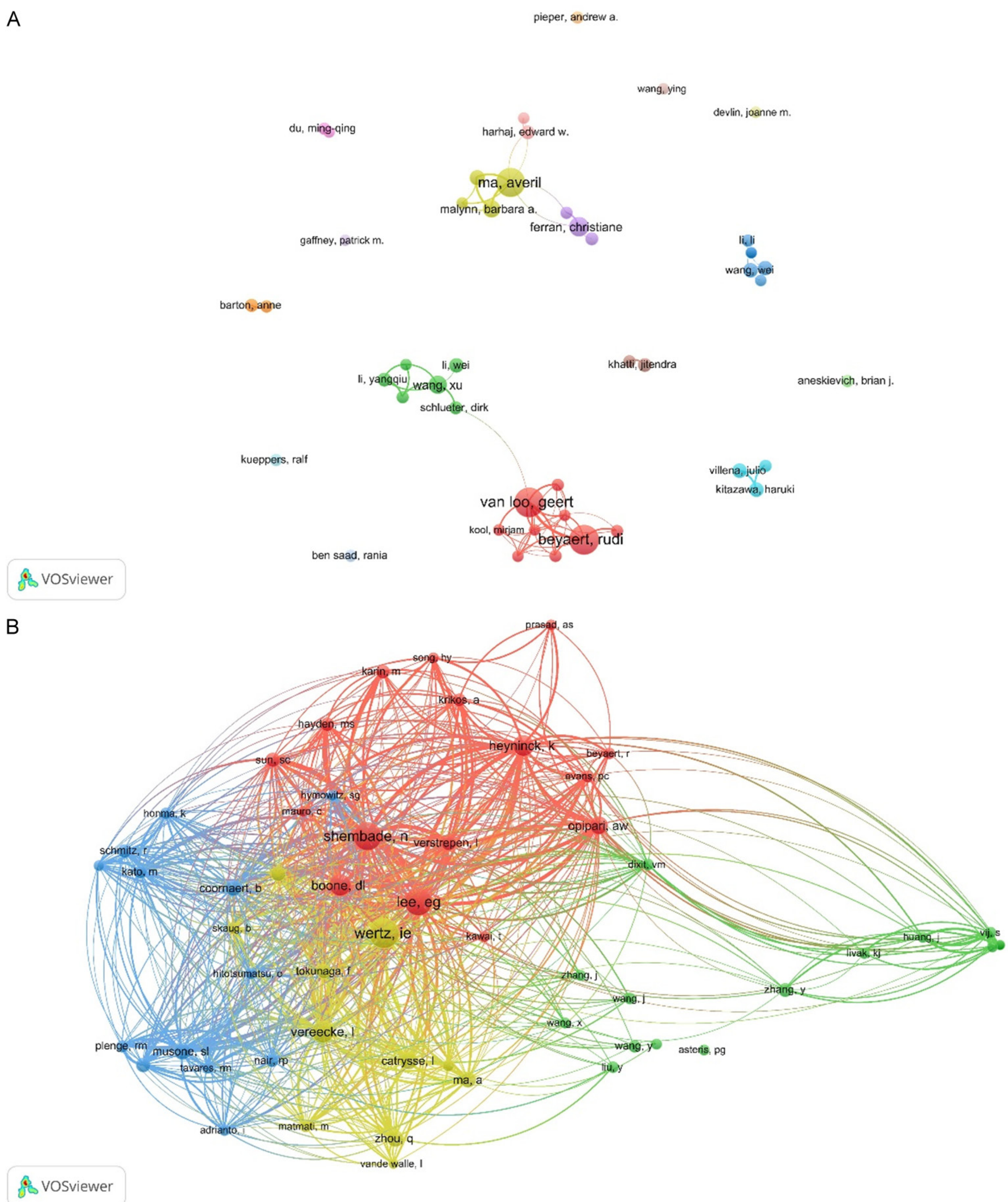


Figure 3. Collaboration networks of authors and co-cited authors in TNFAIP3-related research. A. Author collaboration network visualized using VOSviewer. Each node represents an author, with node size proportional to the number of TNFAIP3-related publications. Lines between nodes indicate co-authorship, and line thickness reflects the strength of the collaboration. B. Co-cited author network generated by VOSviewer. Each node denotes an author, with node size corresponding to the total number of citations. The network illustrates the influence and scholarly prominence of researchers based on co-citation patterns.

Topography of co-citation among journals outlines major pillars of the knowledge base of TNFAIP3 (**Figure 4A**). We have found the Journal of Biological Chemistry (IF = 3.9) to be of paramount importance to store mechanistic information. Although its IF is not great, its 5,753

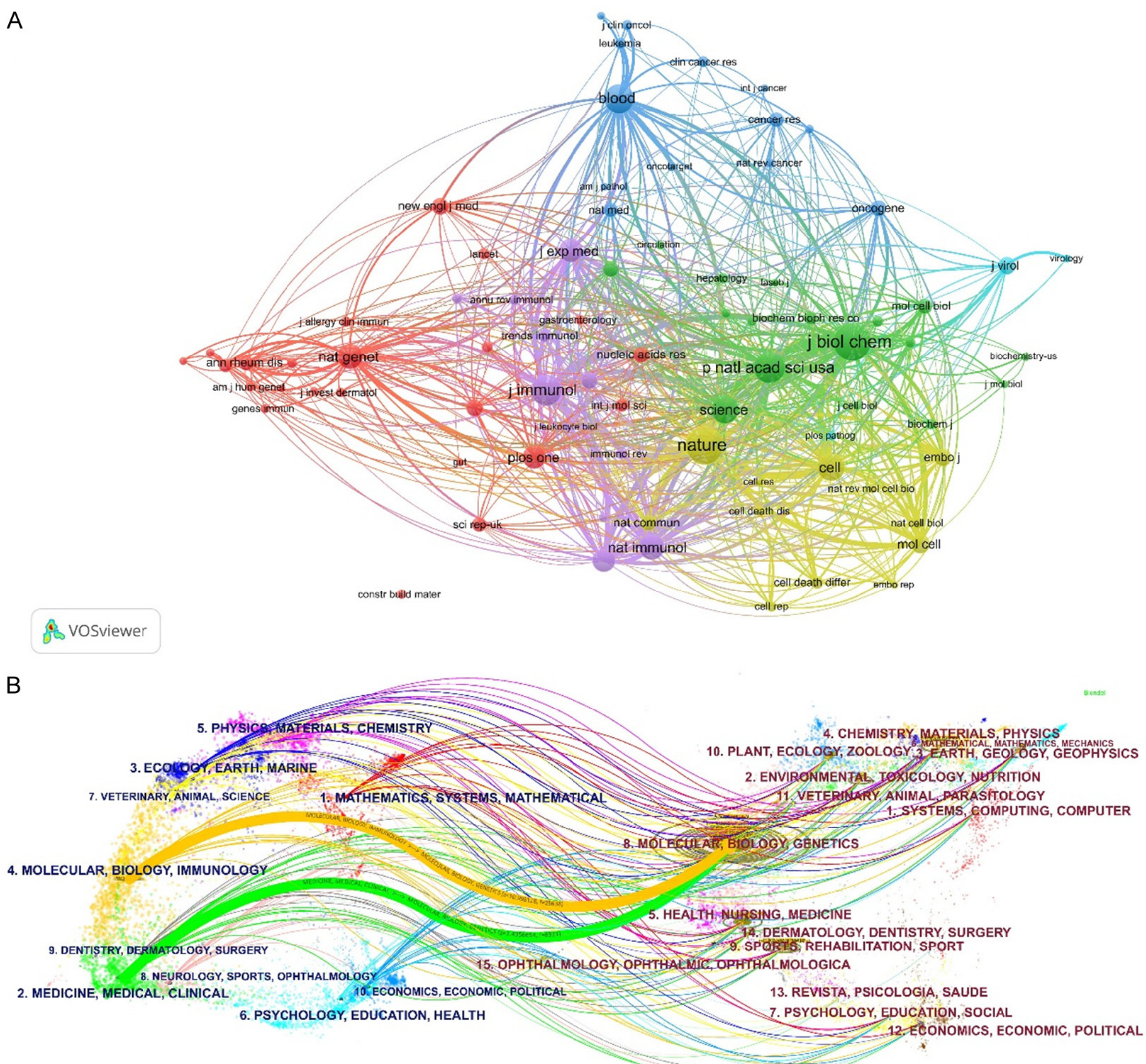


Figure 4. Co-citation network and dual-map overlay of journals in A20-related research. A. The visualization of co-cited journals for A20 studies. Each node in the network graph represents a journal, and the node's size represents the corresponding journal's weight, reflecting its importance in the research field. The connecting lines between the nodes represent the co-citation relationship between the journals, revealing the extent to which they relate to their research topics. The thicker the connecting lines, the higher the intensity of co-citation of these two journals, the stronger the correlation between journals, and the more similar the research topics are. Consequently, the visualization above analyzes the interrelationship between journals and their standing within the academic domain. B. Dual-map overlay of journal citations showing the citing (left) and cited (right) journals, with citation trajectories reflecting disciplinary relationships. The figure was generated by CiteSpace.

citations and close connection through co-citation with Nature (IF = 48.5) serve as the vital link between fundamental biochemistry and discoveries with significant impact. These high centrality hubs such as Cell (IF = 42.5) and PNAS (IF = 9.1) are other core components of this network structure, which serve as major filters and channels of seminal results. These patterns of co-citations provide a profound bibliometric perspective. The intellectual strength of a journal in the A20 is more concerned with the capability of the journal to preserve what is referred to as bedrock scholarship that enables the longevity of academic research rather than the present-day measures of a journal impact.

The dual-map overlay (**Figure 4B**) gives us a macroscopic overview of the intellectual stream that guides in the A20 research area. The main citation pathways (orange and green pathways) define a sound knowledge flow between the core source fields of the study (Molecular, Biology, and Genetics) into the target fields (Molecular, Biology, Immunology, and Medicine, Medical, and Clinical). The fact that this happens is a sign of maturity developing within the field, whereby early molecular descriptions are being used more effectively to solve challenging problems in the field of immunology and clinical practice. Not as an easy transition, this pattern represents a growing interdisciplinary openness. The intensified translational link can be seen by the fact that clinically focused journals are citing cellular-level A20 findings more often. Nevertheless, it would be wise to differentiate between this bibliometric tendency and a fully developed paradigm called the bench-to-bedside paradigm. Despite the growing of the cross-disciplinary discourse, this information indicates some integration stages in which molecular understanding forms the current foundation of, and does not finish, the clinical translation cycle.

Intellectual core and foundational seminal works

The intellectual architecture of the TNFAIP3 domain is anchored by a resilient core of foundational literature, as detailed in Supplementary Table 3. Atop this citation hierarchy lies the work of Lee et al. (2000) which was cited most frequently (641 citations). This groundbreaking article successfully redefined the A20 as a non-redundancy molecular rheostat of NF-kappa B signaling and immune homeostasis. What is presented in this work as the conceptual framework linking A20 to cell fate decision is the main framework through which modern investigators consider autoimmune and inflammatory diseases. Further elaboration of this regulator biochemical complexity was achieved by Wertz et al. (2004) using 607 co-citations which introduced the now-canonical model of the dual catalytic identity of A20. Through its elucidation of both its deubiquitination and E3-ligase properties, this study gave an unchanging mechanistic pattern which continues to contribute to modern molecular studies. It is important to note that the time of publication of all these seminal papers shows what might be called a maturity effect. There are 70 per cent of the top ten citations published before 2010, which means that the discipline has a classical reservoir of knowledge with an overwhelming power to shape the direction of the current A20 research.

The conceptual architecture of A20 research, represented as the co-citation environment (**Figure 5A**), focuses on an intense interaction among the seminal pieces by Lee et al. (2000) and Wertz et al. (2004). The three-fold intellectual triangle supported by the original results of Boone et al. offers the organizational structure of how the regulation of innate immunity is now being viewed. Beyond these static relationships, the citation burst analysis (**Figure 5B**) successfully shows the rate of development of this field and changing priorities. Wertz et al. citations first spike (2005-2009) indicates an era of intense mechanistic fixation as the biochemical nature of A20 was established. It was followed by a strategic adjustment, symbolized by the current burst of citations of Catrysse et al. (2015-2019), indicating the diversification of the study into more systemic aspects of inflammatory conditions.

Surprisingly enough, the fact that various references are still in the active "burst" condition at the end of 2025 emphasizes the ongoing academic interest in the fine details of ubiquitin-mediated signaling (Supplementary Table 4). The persistence of this momentum indicates that the field is shifting towards a detailed and precise approach to immune homeostasis and abandoning the generalized models of signaling.

Keywords and emerging research hotspots

Keyword analysis is a type of cognitive map that helps to decode the thematic development and main foci of the A20 investigation scene [24, 25]. Of an extensive vocabulary of 15,568 distinct words extracted throughout the 3,926 records, we reduced them into a network of 68 high-frequency keywords (greater than or equal to 60 mentions) to illustrate the intellectual structure of the field (**Figure 6A**). This interactive graph indicates the relative size and connectivity of nodes which relate to academic visibility and proximity, respectively. The presence of terms like NF-κB, inflammation and apoptosis suggests a continuing and well entrenched study area that centers on the molecular controls of cellular responses.

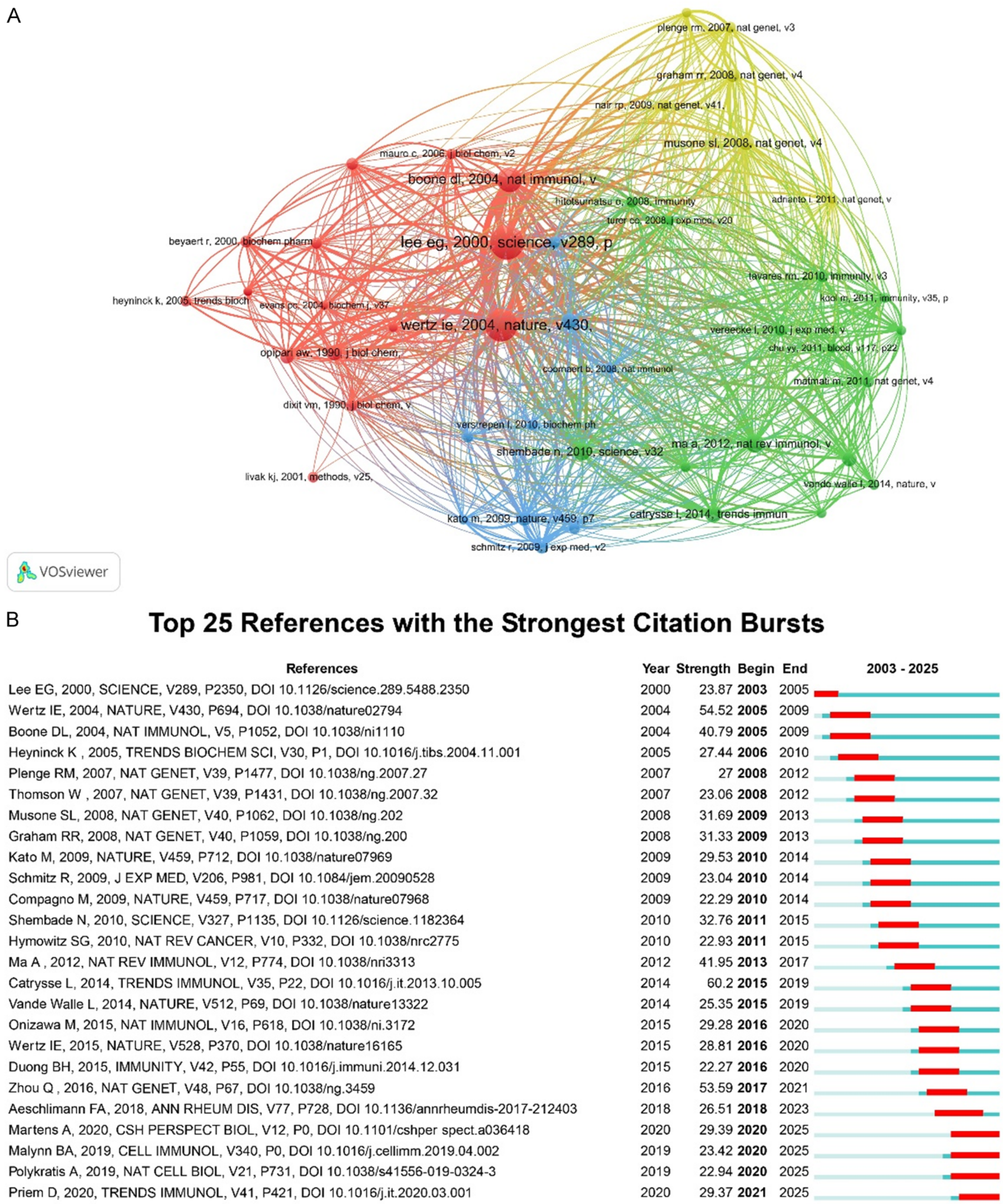
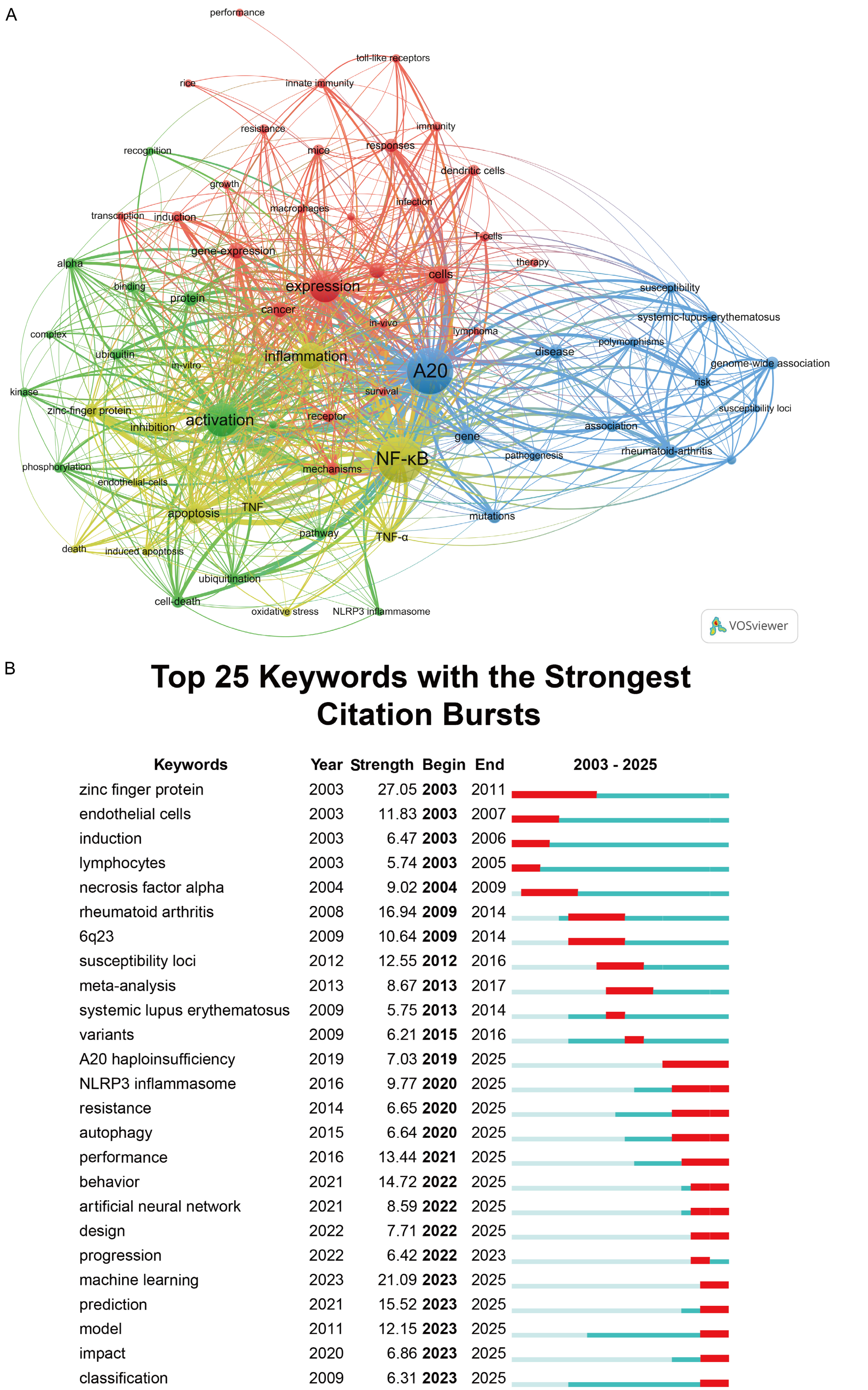


Figure 5. Co-citation network and citation burst analysis of references in A20-related research. A. Co-citation network of references generated using VOSviewer. Each node represents a cited reference, with node size indicating citation frequency and influence within the field. Thicker lines between nodes represent stronger co-citation relationships, suggesting closer topical or conceptual links among the references. B. Citation burst analysis of references visualized using CiteSpace. The horizontal blue line represents the timeline, while red segments indicate periods of intense citation bursts, reflecting emerging interest and high impact during those intervals.

Our network segmentation has defined four functional but related thematic clusters (**Figure 6A** and Supplementary Table 5). An axis of oncology and expression (red): The regulation of A20 activities in malignancy. Inflammatory signaling nexus (yellow): Focuses on the innate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innate immunity
immunity
resistance
mice
responses
recognition
dendritic cells
growth
infection
transcription
induction
macrophages
T-cells
gene-expression
therapy
alpha
cells
expression
susceptibility
binding
protein
cancer
systemic-lupus-erythematosus
in-vivo
lymphoma
complex
polymorphisms
disease
ubiquitin
in-vitro
inflammation
genome-wide association
A20
kinase
risk
survival
susceptibility loci
zinc-finger protein
activation
receptor
inhibition
association
gene
NF-κB
rheumatoid-arthritis
pathogenesis
phosphorylation
mechanisms
endothelial-cells
apoptosis
TNF
mutations
pathway
TNF-α
death
induced apoptosis
ubiquitination
cell-death
oxidative stress
NLRP3 inflammasome
VOSviewer
B
Top 25 Keywords with the Strongest Citation Bursts
Keywords | Year | Strength | Begin | End | 2003 - 2025
zinc finger protein 2003 27.05 2003 2011
endothelial cells 2003 11.83 2003 2007
induction 2003 6.47 2003 2006
lymphocytes 2003 5.74 2003 2005
necrosis factor alpha 2004 9.02 2004 2009
rheumatoid arthritis 2008 16.94 2009 2014
6q23 2009 10.64 2009 2014
susceptibility loci 2012 12.55 2012 2016
meta-analysis 2013 8.67 2013 2017
systemic lupus erythematosus 2009 5.75 2013 2014
variants 2009 6.21 2015 2016
A20 haploinsufficiency 2019 7.03 2019 2025
NLRP3 inflammasome 2016 9.77 2020 2025
resistance 2014 6.65 2020 2025
autophagy 2015 6.64 2020 2025
performance 2016 13.44 2021 2025
behavior 2021 14.72 2022 2025
artificial neural network 2021 8.59 2022 2025
design 2022 7.71 2022 2025
progression 2022 6.42 2022 2023
machine learning 2023 21.09 2023 2025
prediction 2021 15.52 2023 2025
model 2011 12.15 2023 2025
impact 2020 6.86 2023 2025
classification 2009 6.31 2023 2025

Figure 6. Keyword co-occurrence network and thematic evolution of TNFAIP3 research. A. Keyword co-occurrence network generated using VOSviewer. A total of 68 keywords with a minimum occurrence of 60 were clustered into four distinct groups, each represented by a different color (red, green, blue, and yellow), reflecting thematic areas within TNFAIP3 research. B. Citation burst analysis of keywords performed using CiteSpace. The top 25 keywords with the strongest citation bursts are displayed. The blue timeline indicates the full-time span, while red segments denote periods of intense citation activity, marking phases of emerging interest and research focus. The end of a burst period may suggest that the topic has reached a more mature or stabilized stage within the field.

immunity-regulating biochemical cascades. The domain of cell fate and ubiquitination (green): The mechanism of programmed cell death and protein modification. Genetic susceptibility and clinical risk cluster (blue): Exploration of the etiology of TNFAIP3-associated diseases. The structure of these clusters is not isolated. To the contrary, it can be most accurately defined as very penetrable between clusters. Central hub nodes, particularly the words inflammation and expression are important crossroads between distinct thematic domains, which indicates the complicated biological character of A20 as the master integrator of immune homeostasis.

A longitudinal analysis of keyword bursts (**Figure 6B**) can be seen as a strong paradigm shift that marks the evolution of the field by moving out of a state of isolated molecular characterization towards a holistic, system-based view. At the start of the early 2000s, the scientific narrative was mostly focused on the biochemical architecture of the protein. The words zinc finger proteins and induction indicate the reductionist era that would simplify A20 to its most basic elements as an inflammatory signaling cascade. The mechanistic focus then advanced into genomic and medical extension. Instead of explaining the presence of A20, this shifted the focus of the study to explain where and when its malfunction happens within the pathological space of humans. Nevertheless, this shift is marked by the popularity growth of the key words connected with different autoimmune spectra: systemic lupus erythematosus and psoriasis. It signifies a strategic movement toward clinical relevance of TNFAIP3, whereby scientists tried to bridge the gap between the simple molecular mechanisms and the genetics of multifactorial autoinflammatory illnesses.

At the close of 2025, A20 research is at a pivot where biochemical detail intersects with the integration of systems. The most recent frontier can be defined as the higher complexity of the regulation axes at multiple levels, especially the cross talk between the pyroptosis triggered by NLRP3, and the autophagic flux. This transition implies that A20 can no longer be regarded as an autonomous inhibitor but as a rheostat in an expanded cellular quality control system. Alongside the mechanistic investigation, the field is experiencing a high-intensity computational paradigm shift. Artificial intelligence (AI) and advanced classification models have started to transform the prediction ability of the field by going past descriptive observation to predicting the course of the disease and its medical response to treatment on the basis of data. Overall, all these tendencies demonstrate that A20 studies have passed the stage of maturity when mechanistic accuracy comes along with the might of computational synthesis in order to direct upcoming translational therapies.

Collaboration networks across countries and institutions

The cross-border synergy in A20 research exhibits a multifaceted network architecture, as visualized in the geographic clusters of countries with ≥ 5 publications (Supplementary Figure 2A). In our analysis, we have found that Germany was the largest collaborative hub, and it remains engaged in the scientific diplomacy of 49 countries. Such a significant level of extensibility is also matched by the United States (48), England (47) and Japan (40), whereas China (38) also exhibits a strong but more compact international exposure.

We then divided the geopolitical structure of the field into three main collaborative currents. Sino-US Bilateral Axis: It is characterized by a very high level of strategic interdependence and acts as the leading driver of world volume. Transatlantic-Belgian Nexus: It is a tripartite synergy between Germany, US, and the UK, with Belgium playing a pivotal role as a mechanistic bridge between Europe. Japanese-Pacific Integration: It is a specific network that was initiated by Japan which effectively spans old-style Western alliances (the US and Germany) with emergent regional alliances, most significantly, the Argentine alliance. Taken together these patterns imply that although the A20 domain has its foundation in Western scholarly customs, it is progressively being characterized by a multi-polar fabric of knowledge transfer.

A granular investigation of the institutional topography (more than 20 publications) found that University of California, San Francisco (UCSF) is the most highly linked hub of the field and it coordinates a web of 27 individual organizational associations (Supplementary Figure 2B). Such a high level of centrality is matched by major regional hubs in Asia, particularly Sun Yat-sen University (22 partners) and the Chinese Academy of Sciences (20 partners), which are important keystones of large-scale research projects. Further insights into such patterns of collaboration indicate an international outreach strategy. Although the Chinese research network has essentially remained US focused with intense bilateral interaction, European institutions have managed to establish a much more diverse and varied international presence. All these organizational forces together outline a research scene, which is defined by a healthy interconnection between US and China that has become even more stable due to a strong European academic nexus and more purpose driven regional relationships in Asia.

Summary of mechanistic and translational frontiers

The modern A20 research paradigm has consolidated around three domains that are functionally interconnected and determine the limits of the discipline at present. The biochemical dissection of A20 enzymatic duality, specifically its interaction between deubiquitinase and E3 ligase abilities, forms the most important regulatory axis to regulate canonical NF-κB signaling and its resultant inflammatory cascades [21]. It is getting more mechanistically intricate. More recent investigations have been exploring the part played by A20 as a molecular rheostat in damping down NLRP3 inflammasome activation [8]. Consistent with these findings, clinical definition of HA20 has yielded a definite human paradigm, demonstrating how quantitative lack of proteins can be translated into system autoinflammatory symptoms.

From such a mechanistic core, research is diversifying swiftly into an ever-widening range of pathology [12, 26, 27]. Not limited to traditional immunology, A20 dysfunction is currently being identified as a key player in oncogenesis, chemoresistance, and the preservation of tissue-specific homeostasis by modulation of autophagy [28-31]. The continued interest in crosstalk between A20 and programmed cell death pathways indicates that it is shifting towards context-dependence which is a necessary condition on the path to effective therapeutic interventions [3, 32].

Finally, the A20 knowledge base is undergoing a strategic computational change. There is a new translational frontier that has been opened up by the combination of high dimensional multi-omics datasets and machine learning systems to assist in narrowing the gap between the discoveries made at the bench and the bedside application of them. Although these computational frameworks are not yet explored, they show the potential of bringing A20 together with precision medicine. Future attempts are likely to be successful only when we can resolve the spatiotemporal intricacies of the regulation of A20 and eventually transform these complex mechanistic observations into practical diagnostic kits and individualized treatment interventions.

Discussion

Twenty years in the academic world is not just about the simple accumulation of data regarding TNFAIP3 research. TNFAIP3 research represents a major shift with A20 as a relatively new mechanistic puzzle into a key homeostatic rheostat of modern immunology. As we mapped longitudinally, we observed exponential growth in the number of publications that are currently at a critical inflection point over the last five years. This explosion is not a statistical occurrence alone but also shows a worldwide move toward heuristics regarding decoding the intricate regulatory pathways of innate immunity, inflammation and the intricacies of antiviral defense.

More specifically, it can be stated that such a wave of academic work means changing the conceptual framework of the field. The focus of the study has been redirected to the initial reductionist disassembly of the A20 ubiquitin-editing enzymes to an in-depth understanding of its systemic impact. Rather than viewing A20 signaling as an independent process, the modern field now places greater worth on how its slight fluctuations group together heterogeneous disease phenotypes and determine the efficacy of clinical interventions. Due to this shift between a general characterization and pathological processes, it also underscores the growing significance of the proteins, as the main targets, in the age of precision rheumatology.

Biochemically, A20 is not a monolithic inhibitor, but it is a multifunctional checkpoint that controls the cross-talk between innate signals and adaptive responses and programmed cell transformations. Regarding innate signaling, A20 acts as an intermediary of timely termination of NF-kappa B pathways induced by TNF, TLR, and IL-1 receptors [33-35]. It is done through an exceptionally specific and enzymatic redesigning of the ubiquitin structures surrounding the key scaffolding proteins, particularly RIPK1 and TRAF6, which prevents the conversion of physiological defense into pathological over-inflammation [36].

Apart from innate sensing, A20 is a critical gatekeeper of adaptive immune homeostasis. Through its control over the activation levels of T- and B-cell populations, it ensures that the rate of lymphocyte responses is kept within the range of tolerance, and the development of autoimmunity is essentially prevented [22, 35, 37]. Possibly the most important thing is that modern comprehension of A20 has shifted to the field of cell-fate control. A20, in conjunction with RIPK1-mediated apoptosis, necroptosis, and the NLRP3-pyroptotic pathway, serves as a context-specific tissue survival switch [7, 38]. Such interconnected roles indicate that A20 is not just an anti-inflammatory drug but a master regulator that provides proteostatic equilibrium with cellular prosperity in various pathological scenarios.

The research on A20 demonstrates a sophisticated equilibrium between quantitative production and qualitative influence. Although China is growing its publication volume at impressive rates, the intellectual backbone of the field still lies within the pioneering Western institutions. UCSF, Ghent University and Harvard have maintained significant first-mover effects since their initial mechanistic studies on the deubiquitination of A20 form the canonical reference point of the contemporary citation metrics. The cooperation patterns are also diverse: Chinese research networks are characterized by regional clustering, and the Euro-American axis is characterized by high cross-border integration. It is believed that this gap indicates that emerging clusters ought to move away from productivity-related models toward intellectual leadership.

Journal structure and co-citation structure provides an extremely detailed insight into the way TNFAIP3 information spreads across the biomedical hierarchy. The initial mechanistic reports have attracted much attention in specific immunology and molecular biology publications, such as The Journal of Immunology, Blood and JBC. They serve as the authoritative records of NF-κB- and ubiquitin-based regulatory models. Notably, the two-map overlaid model reveals a one-way knowledge pipeline whereby experimental molecular findings are progressively used to influence clinically oriented fields. The downstream direction of this flow indicates that the A20 research is not isolated in fundamental biochemistry anymore, but is actively driving the translational development of the field into patient-centered models.

The modern A20 landscape is based on three thematic hubs which are inherently interconnected and cannot be easily categorized. Being a feedback orchestra hub, A20 is perceived as an inducible molecular rheostat which can tune the kinetic signature of both NF-κB and cytokine signals to the most basic level [1-3]. Being a cell-fate integrity hub, the new expanding field has situated A20 in the center of regulated cell death. The interaction between RIPK1, RIPK3 and the NLRP3 inflammasome makes A20 act as a central switch regulating the shift of inflammation to apoptosis, necroptosis, or pyroptosis [1, 4, 5], a finding of significant importance to organ specific autoimmunity. Being a genomic and precision medicine hub, in addition to pathway biology, the development of the HA20 and TNFAIP3 mutations has moved the field of research into the area of clinical genetics [14-16]. In this case, A20 is not a signaling medium, it now has become a diagnostic pillar, which requires incorporation into the risk stratification and genetic counseling of early-onset autoinflammatory syndromes.

As we have demonstrated through our bibliometric mapping, the clinical significance of A20 is based on the fact that it has the ability to counteract different, though mechanistically related pathologies. Genetic polymorphisms or decreased TNFAIP3 expression is not just correlatively associated with the disease in SLE and RA; rather, they are triggers that induce the cytokine storm driven by NF-κB and amplify the proliferation of autoreactive lymphocytes. Equally, A20 acts as an obligatory protector of the mucosal barrier integrity within the gastrointestinal microenvironment, and its failure to do so in the epithelial and myeloid compartment leads to a loss of the tolerance of homeostasis that leads to perpetuation of the chronic relapsing inflammatory process which characterizes IBD. HA20 discovery is the final genetic proof of this model indicating that even a quantitative reduction in A20 function is enough to circumvent the regulatory redundancies and cause early-onset systemic autoinflammatory diseases.

The clinical contexts confirm that the hotspots that we have obtained within our analysis, i.e. ubiquitination, NLRP3 and cell death, are not individual statistical groups but components of a cohesive biochemical axis. As illustrated in **Figure 7**, A20 is a high-fidelity ubiquitin-editing checkpoint located below TNF, TLR, and IL-1R signaling [35, 39, 40]. Through regulation of the enzymatic reorganization of K63- and K48-linked ubiquitin chains of critical adaptors such as RIPK1, TRAF6, and NF-κB essential modulator (NEMO), A20 develops a level of gene transcription of inflammatory genes, which cannot shift the acute physiological reaction to chronic tissue damage.

One of the main results of the longitudinal literature study is that the biological nature of A20 is essentially dualistic. As its function as an anti-inflammatory brake has been reported in autoimmunity, its conduct in oncology is often more winding and specific to the situation. A20 may act as a tumour suppressor in certain cancers by blocking the inflammation-induced pro-tumorigenic events as well as genomic stability. Nevertheless, A20 activity in mature tumors could exert a paradoxical effect on malignant survival. By helping to conceal cancer cells to apoptotic or necroptotic signals, A20 can enhance immune evasion and confer resistance to cytotoxic therapy.

This operational dichotomy, shown in **Figure 8**, demonstrates how A20 is involved in the precarious balance between inflammatory responses and controlled cell death [1, 39, 40]. A20 has other functions beyond the control of transcription as a molecular judge in which one outcome is chosen over others and the choice is the repression of programmed death induced by RIPK1 and pyroptosis initiated by NLRP3. The fact that it controls both processes is the reason why it may be associated with a wide range of phenotypes, as its dysfunction can cause autoinflammation and tissue damage or allow the survival of therapy-resistant clones. This is also important because it indicates that specific tissue approaches should be used when considering the A20 pathway in clinical practice.

The modern direction of TNFAIP3 research can be described as the inclination towards translational edge. The spatiotemporal increase in burst citations of concepts like HA20, NLRP3 inflammasome and chemoresistance indicates a growing desire to investigate A20 activity as a therapeutic modifier in relation to both biologics and small molecule treatment strategies [10, 13, 17, 22]. The latest findings in the fields of neuroinflammation and hematology propose that A20 signaling is spatiotemporally granular and a vital determinant of whether shared inflammation pathways are resolved or deviate into clinically heterogeneous phenotypes.

Such mechanistic deepening is now being coordinated with a very significant computational reorientation. Combining artificial neural networks and machine-learning models suggests that an attempt is made to exploit A20-regulatory networks in prognostic stratification. In particular, the combination of high-dimensional transcriptomic and clinical samples permits preliminary disease subtyping and prediction of therapeutic relapse [41]. However, the

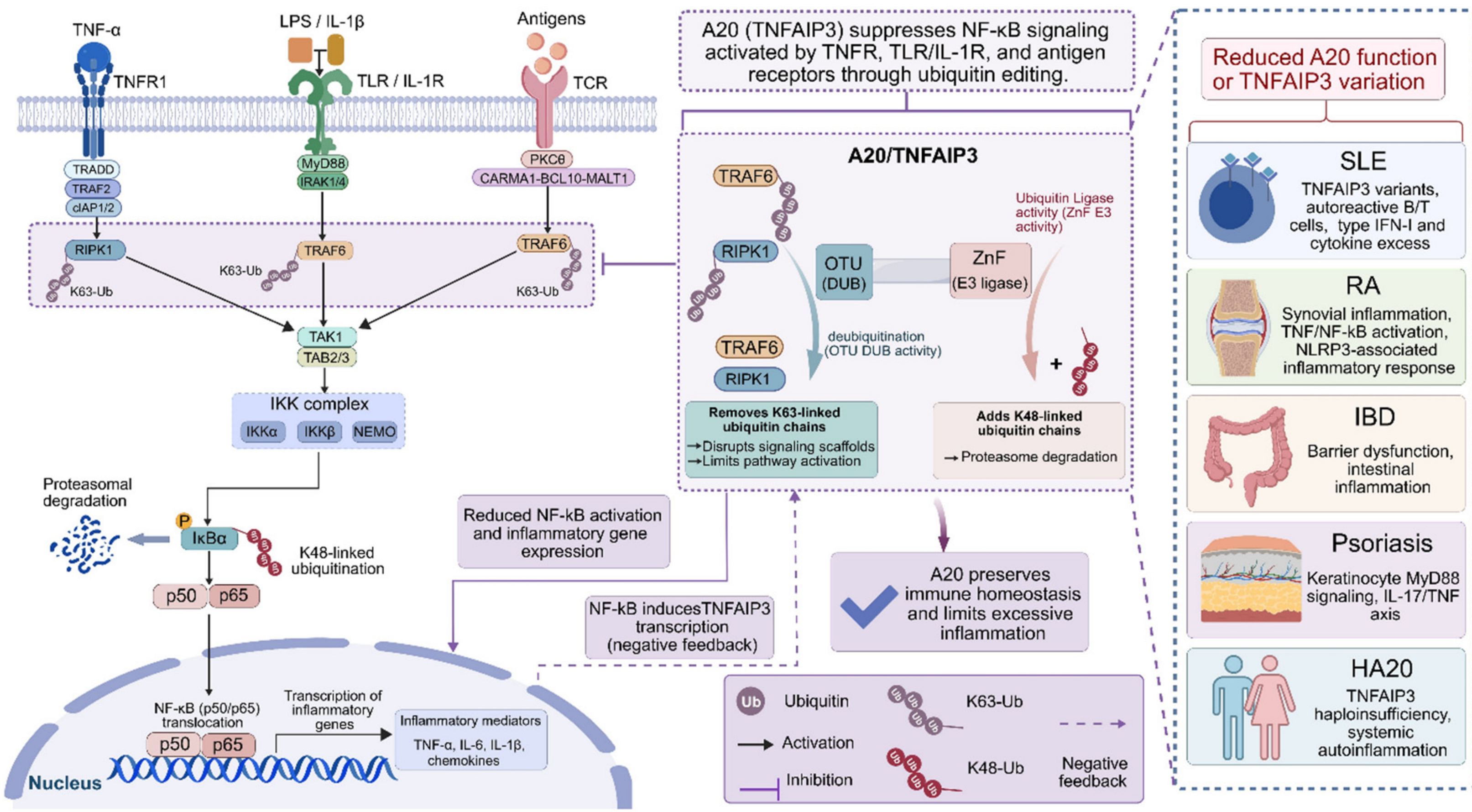

Figure 7. Mechanistic role of A20/TNFAIP3 in autoimmune disease signaling. This schematic illustrates how A20/TNFAIP3 functions as a central ubiquitin-editing checkpoint in autoimmune and inflammatory signaling. Upstream stimulation by TNF-α/TNFR1, TLR/IL-1R ligands, or TCR signaling promotes the assembly of adaptor complexes involving RIPK1, TRAF6, MyD88, IRAK1/4, and related signaling intermediates. These events induce K63-linked ubiquitination and activate the TAK1-IKK-NF-κB axis, leading to IκBα phosphorylation and degradation, NF-κB nuclear translocation, and transcription of inflammatory mediators, including TNF-α, IL-6, IL-1β, and chemokines. A20, encoded by TNFAIP3, restrains these pathways through its dual ubiquitin-editing functions: its OTU deubiquitinase domain removes K63-linked ubiquitin chains, whereas its zinc-finger E3 ligase/ubiquitin-editing activity promotes K48-linked ubiquitination and signal termination. Reduced A20 function or TNFAIP3 variation may therefore amplify NF-κB-dependent inflammatory responses and contribute to disease-associated immune dysregulation in systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, psoriasis, and A20 haploinsufficiency. This schematic was generated based on established mechanistic models of A20/TNFAIP3-mediated ubiquitin editing, NF-κB suppression, and disease-associated immune dysregulation [22, 39, 40].

A20 (TNFAIP3) in autoimmunity and inflammation

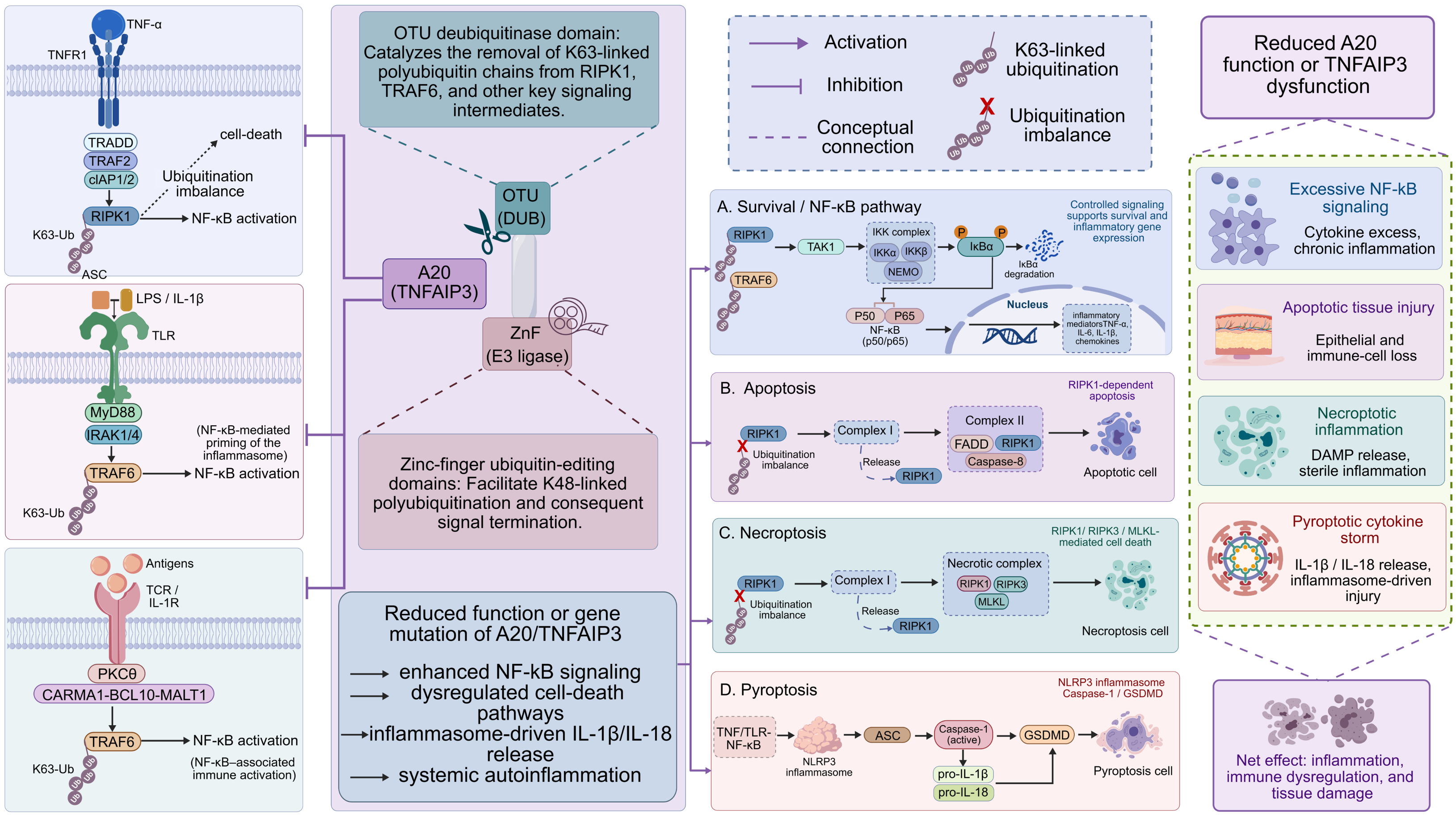

Figure 8. A20 at the interface of inflammation and regulated cell death. This schematic illustrates the multifaceted role of A20 in integrating innate immune signaling, adaptive immune responses, ubiquitin editing, autophagy, and regulated cell death. In innate immune pathways, TLR and TNFR activation engage adaptor molecules such as TRIF, TRAF3, TRAF6, RIPK1, and TRAF2/5, leading to IKK activation and downstream NF-κB signaling. A20 restrains these pathways through deubiquitylation and ubiquitin-editing mechanisms, thereby limiting excessive inflammatory activation. In adaptive immunity, A20 modulates TCR and BCR-associated signaling by regulating RIPK1/TRAF6-dependent NF-κB activation, contributing to the maintenance of lymphocyte homeostasis and preventing autoimmune or excessive inflammatory responses. Beyond immune signaling, A20 also acts as a central regulator of cell death pathways. By controlling RIPK1/RIPK3/MLKL signaling, A20 limits necroptosis. By regulating RIPK1/ASK1- and cIAP-associated signaling under pathological conditions, A20 influences apoptosis. By suppressing TLR/NF-κB-related inflammatory priming, A20 constrains pyroptosis. These functions collectively position A20/TNFAIP3 as a key ubiquitin-editing checkpoint that preserves immune homeostasis, prevents uncontrolled inflammation, and limits inflammation-associated cell death. Symbols indicate deubiquitylation, ubiquitylation, and autophagy. This schematic was generated based on established mechanistic models linking A20/TNFAIP3-mediated ubiquitin editing to innate and adaptive immune regulation, NF-κB suppression, autophagy modulation, and inhibition of regulated cell death pathways [1, 4, 39, 40].

present state of A20 research on digital devices is still in its avant-garde state, and the field continues to be challenged by retrospective designs, small sample sizes, as well as the lack of multi-center verifications. Therefore, at this point, A20 ought to be considered as one of the potential indicators in biomarker signatures and risk-stratification systems, but not as an independent index of standard clinical management.

Through the synthesis of 20+ years of bibliometric information, the study places A20 not only as an inhibitor of signaling but as a multimodal homeostatic hub controlling the complex overlaps of inflammatory resolution, cellular viability, and immune tolerance. This domain has a specific pattern of longitudinal development which is asymmetrical. The legacy of well-known intellectual Western research centers can still adjust the mechanistic level of the field, however, the explosive growth of the investigative power of China creates the critical mass needed to conduct large-scale discovery and clinical application.

To decode these trends of global research gives a strategic direction of the funding agencies and scientific community in promoting more cooperative transnational partnerships. The field is at a crucial stage where it can turn over describing associations into detailed mechanistic and interventional research. Finally, we will be clinically effective in targeting A20 only when we have broken down the situational logic of its regulatory action. Particularly, what dictates the functional outcomes of the tissue-specific environment and temporal fluxes are the necessary and crucial preconditions of successful therapeutic manipulation by A20 in the context of precision medicine.

Limitations and future directions

Our research has a number of limitations. Firstly, limiting the data to that which is WoSCC selected, due to its high compatibility with bibliometric programs, might introduce selection bias when leaving out papers that are specific to Scopus or PubMed. This is why these results are mainly applicable to the index of the WoSCC. Secondly, the final cut-off date (December 31, 2025) and use of the cumulative citation measure creates a time delay, possibly missing some highly innovative articles released in the past few years. Also, our macroscopic analysis of networks does not show detailed experimental trends but general themes. Hence, we suggest interpreting our results as being related to the WoSCC-indexed A20 literature instead of the full global literature.

The future studies ought to incorporate a variety of sources such as Scopus and PubMed and should be augmented by full-text semantic mining to address the experimental subtleties which typical metadata may not reflect. Integration of multi-omics datasets based on a machine learning framework is still important in order to validate A20-associated signatures as powerful clinical biomarkers. Moreover, the auditing of funding environments by using a specific repository of grants will be necessary to define the structural and economic reasons why this area of research continues to grow.

Conclusion

This paper presents the ultimate layout of the A20 research path on a worldwide scale between 2003-2025. This research discipline has been changing dramatically over time as it has combined classical molecular pathways and new clinical problems like HA20 and therapy resistance. Although the maturity of the research environment has occurred, the focus of scholarly power still exhibits a geographical bias, indicating that additional collaborative networks are necessary. Taken together, our observations support the view that A20 is an important gatekeeper of immune and inflammatory routes and that its functional regulation should be prioritized in the coming ten years of translational research into autoimmune and inflammatory disorders.

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Disclosure of conflict of interest

None.

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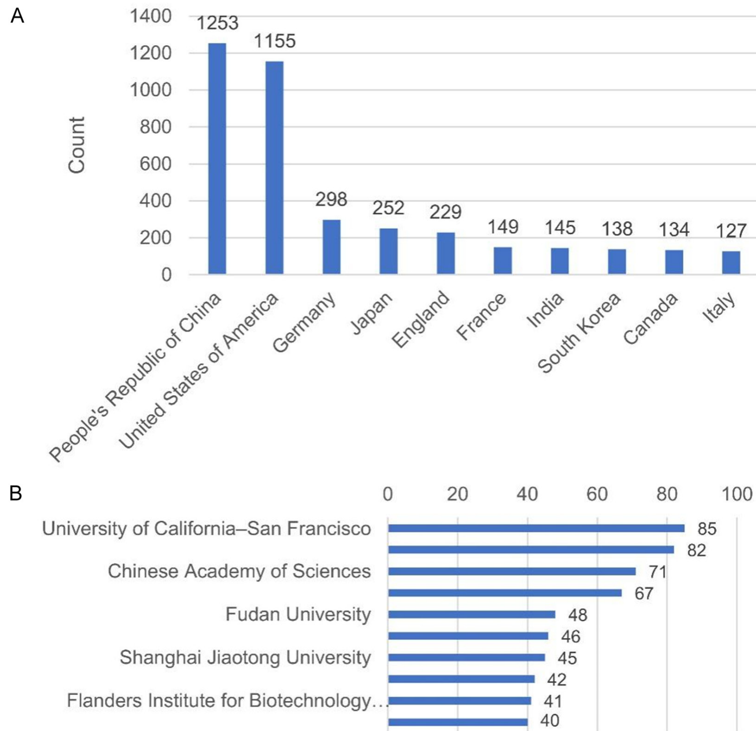


Supplementary Figure 1. Global research output on TNFAIP3 (2003-01-01 to 2025-12-31): top 10 productive countries and institutions. A. Bar chart displaying the top 10 countries ranked by the total number of TNFAIP3-related publications retrieved from the Web of Science Core Collection. B. Bar chart showing the top 10 institutions based on publication volume in TNFAIP3-related research from January 1, 2003, to December 31, 2025.

Supplementary Table 1. Top authors and co-cited authors contributing to TNFAIP3 studies in autoimmunity and inflammation (2003-01-01 to 2025-12-31)

Rank	Author Name	Affiliation (Current or Major)	Number of Publications	Total Citations	H-index	Average Citations per Article	Co-Cited Author	Affiliation (Current or Major)	Citations
1	Geert van Loo	Ghent University, Belgium	52	4934	33	94.88	Ingrid E Wertz	Genentech, Inc., USA	749
2	Rudi Beyaert	Ghent University, Belgium	51	6205	36	121.67	Noula Shembade	University of Miami, USA	663
3	Averil Ma	University of California, San Francisco, USA	49	5547	34	113.20	Eric G Lee	University of California at San Francisco, USA	641
4	Christiane Ferran	Harvard Medical School, USA	25	709	15	28.36	Lars Vereecke	Ghent University, Belgium	465
5	Xu Wang	Jinan University, China	22	424	14	19.27	David L Boone	University of California, Davis, USA	419
6	Barbara A. Malynn	University of California, San Francisco, USA	21	2473	17	117.76	Karen Heyninck	Ghent University, Belgium	413
7	Rommel Advincula	University of California, San Francisco, USA	16	1923	13	120.19	A W Opipari	University of Michigan Medical School, USA	320
8	Haruki Kitazawa	Tohoku University, Japan	15	749	11	49.93	Leen Catrysse	Ghent University, Belgium	303
9	Julio Villena	Tohoku University, Japan	15	749	11	49.93	S L Musone	University of California San Francisco, USA	279
10	Yan Wang	Qingdao University	15	427	10	28.47	Qing Zhou	Zhejiang University, China	270

Authors are ranked by the number of TNFAIP3-related publications in the field of autoimmunity and inflammatory diseases from 1 January 2003 to 31 December 2025. Co-cited authors were ranked based on the total number of citations of TNFAIP3-related publications in the field of autoimmunity and inflammation from 1 January 2003 to 31 December 2025. The publication volume, total citation count, and H-index were obtained for each individual through the “Citation Report” function in Web of Science. Affiliation reflects the most recent or most frequently listed institutional affiliation across included publications.

Supplementary Table 2. Most active journals and co-cited journals publishing TNFAIP3-related research in autoimmunity and inflammation (2003-01-01 to 2025-12-31)

Rank	Journal Name	Number of Publications	Total Citations	Average Citations per Article	Latest JCR impact factor	H-index	Co-cited Journal	Co-citation	2025 Impact Factor
1	PLOS ONE	111	2918	26.29	2.6	33	JOURNAL OF BIOLOGICAL CHEMISTRY	5753	3.9
2	FRONTIERS IN IMMUNOLOGY	83	1915	23.07	5.9	26	NATURE	5712	48.5
3	SCIENTIFIC REPORTS	70	1188	16.97	3.9	21	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	4182	9.1
4	JOURNAL OF BIOLOGICAL CHEMISTRY	63	4807	76.30	3.9	39	JOURNAL OF IMMUNOLOGY	4128	3.4
5	JOURNAL OF IMMUNOLOGY	54	3302	61.15	3.4	33	BLOOD	3781	23.1
6	INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	47	526	11.19	4.9	13	CELL	3385	42.5
7	BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS	46	1254	27.26	2.2	21	SCIENCE	3363	45.8
8	BLOOD	33	2883	87.36	23.1	27	NATURE GENETICS	2968	29
9	ONCOTARGET	31	765	24.68	0	18	NATURE IMMUNOLOGY	2911	27.6
10	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	27	2033	75.30	9.1	21	JOURNAL OF EXPERIMENTAL MEDICINE	2610	10.6

Journals are ranked by the number of TNFAIP3-related publications in the field of autoimmunity and inflammation between 2003-01-01 and 2025-12-31. Co-cited journals were ranked based on the total number of citations of TNFAIP3-related publications in the field of autoimmunity and inflammation from 1 January 2003 to 31 December 2025. Citation metrics were extracted from the Web of Science Core Collection. Journal impact factors were obtained from the latest officially released edition of Journal Citation Reports. The H-index reflects the citation impact of TNFAIP3-related publications attributed to each journal within the retrieved dataset.

Supplementary Table 3. Top 10 most-cited TNFAIP3-related papers in autoimmunity and inflammation (2003-01-01 to 2025-12-31)

Rank	First Author (Year)	Title	Journal Name	Citations	DOI
1	Lee EG, 2000	Failure to regulate TNF-induced NF-kappaB and cell death responses in A20-deficient mice [1]	Science	641	https://doi.org/10.1126/science.289.5488.2350
2	Wertz IE, 2004	De-ubiquitination and ubiquitin ligase domains of A20 downregulate NF-kappaB signalling [2]	Nature	607	https://doi.org/10.1038/nature02794
3	David L Boone, 2004	The ubiquitin-modifying enzyme A20 is required for termination of Toll-like receptor responses [3]	Nature Immunology	409	https://doi.org/10.1038/ni1110
4	Averil Ma, 2012	A20: linking a complex regulator of ubiquity-lation to immunity and human disease [4]	Nature Reviews Immunology	259	https://doi.org/10.1038/nri3313
5	Noula Shembade, 2010	Inhibition of NF-kappaB signaling by A20 through disruption of ubiquitin enzyme com-plexes [5]	Science	255	https://doi.org/10.1126/science.1182364
6	Leen Catrysse, 2014	A20 in inflammation and autoimmunity [6]	Trends in Immunology	241	https://doi.org/10.1016/j.it.2013.10.005
7	Lars Vereecke, 2009	The ubiquitin-editing enzyme A20 (TNFAIP3) is a central regulator of immunopathology [7]	Trends in Immunology	224	https://doi.org/10.1016/j.it.2009.05.007
8	S L Musone, 2008	Multiple polymorphisms in the TNFAIP3 region are independently associated with systemic lupus erythematosus [8]	Nature Genetics	212	https://doi.org/10.1038/ng.202
9	A W Opipari, 1990	The A20 cDNA induced by tumor necrosis fac-tor alpha encodes a novel type of zinc finger protein [9]	Journal of Biological Chemistry	208	https://doi.org/10.1016/S0021-9258(18)77165-2
10	Qing Zhou, 2016	Loss-of-function mutations in TNFAIP3 leading to A20 haploinsufficiency cause an early-onset autoinflammatory disease [10]	Nature Genetics	200	https://doi.org/10.1038/ng.3459

The table lists the top 10 most-cited original research articles and reviews related to TNFAIP3 in the context of autoimmune and inflammatory diseases, based on citation counts from the Web of Science Core Collection as of 31 December 2025. These articles represent seminal works that have significantly influenced the field.

Supplementary Table 4. The details of the 25 references in which the citation burst occurred

Rank	Strength	Main research content
1	23.87	A20 plays a crucial role in modulating the inflammatory response by terminating the TNF-induced NF-κB signaling pathway and suppressing cell death [1].
2	54.52	A20 suppresses NF-κB activation through its dual ubiquitin-editing activities on RIP proteins [2].
3	40.79	A20 regulates TNF-independent inflammation by deubiquitinating TRAF6 to inhibit TLR-NF-κB signaling [3].
4	27.44	A20 inhibits NF-κB activation through its dual ubiquitin-editing activities on RIP, thereby suppressing inflammation and cancer development [11].
5	27	Two independent RA susceptibility loci were identified at 6q23 near TNFAIP3 (rs10499194 and rs6920220) [12].
6	23.06	The WTCCC confirms that the 6q23 SNP rs6920220 (OLIG3-TNFAIP3) is significantly associated with RA ($P = 1.1 \times 10^{-8}$) [13].
7	31.69	Variants in TNFAIP3 contribute to SLE pathogenesis through A20-mediated immune regulation [8].
8	31.33	Variants in TNFAIP3, including rs5029939, confer differential disease risks for SLE ($P = 2.89 \times 10^{-12}$) and RA [14].
9	29.53	A20 inactivation via somatic mutations/deletions drives B-cell lymphomagenesis by unleashing NF-κB signaling [15].
10	23.04	Biallelic A20 inactivation promotes cHL/PMBL pathogenesis via NF-κB dysregulation, with higher frequency in EBV (-) than EBV (+) cHL (44% vs 12.5%) [16].
11	22.29	Genetic lesions in multiple negative and positive regulators of NF-κB underlie its constitutive activation and drive lymphomagenesis in diffuse large B-cell lymphoma [17].
12	32.76	A20 terminates NF-κB signaling through the degradation of E2 ubiquitin-conjugating enzymes [5].
13	22.93	The ubiquitin-editing enzyme A20 links chronic inflammation to cancer development by modulating inflammatory signaling pathways [18].
14	41.95	A20 modulates ubiquitin signaling pathways in inflammation and cancer [4].
15	60.2	A20 maintains tissue homeostasis through ubiquitin-mediated regulation of inflammatory signaling pathways [6].
16	25.35	A20 deficiency drives the development of rheumatoid arthritis via the NLRP3-IL-1β axis [19].
17	29.28	A20 prevents necroptosis by deubiquitinating RIPK3 at Lys5, thereby disrupting RIPK1-RIPK3 complex formation [20].
18	28.81	Phosphorylated A20 orchestrates ubiquitin editing to balance inflammation and cell death [21].
19	22.27	A20 suppresses the NLRP3 inflammasome by inhibiting RIPK3-dependent pro-IL-1β ubiquitination at Lys133 [22].
20	53.59	Haploinsufficiency of A20 drives autoinflammation [10].
21	26.51	A20 haploinsufficiency (HA20) is associated with early-onset recurrent ulcers and a heterogeneous clinical spectrum [23].
22	29.39	A20 modulates inflammation via NF-κB and cell death regulation, with mutations linked to autoimmune diseases [24].
23	23.42	A20 prevents disease development by modulating ubiquitin signaling pathways [25].
24	22.94	A20 prevents inflammasome-driven arthritis by ZnF7-mediated inhibition of macrophage necroptosis through the RIPK1-RIPK3-MLKL axis [26].
25	29.37	A20's dual anti-inflammatory mechanisms: ubiquitin editing and suppression of cell death [27].

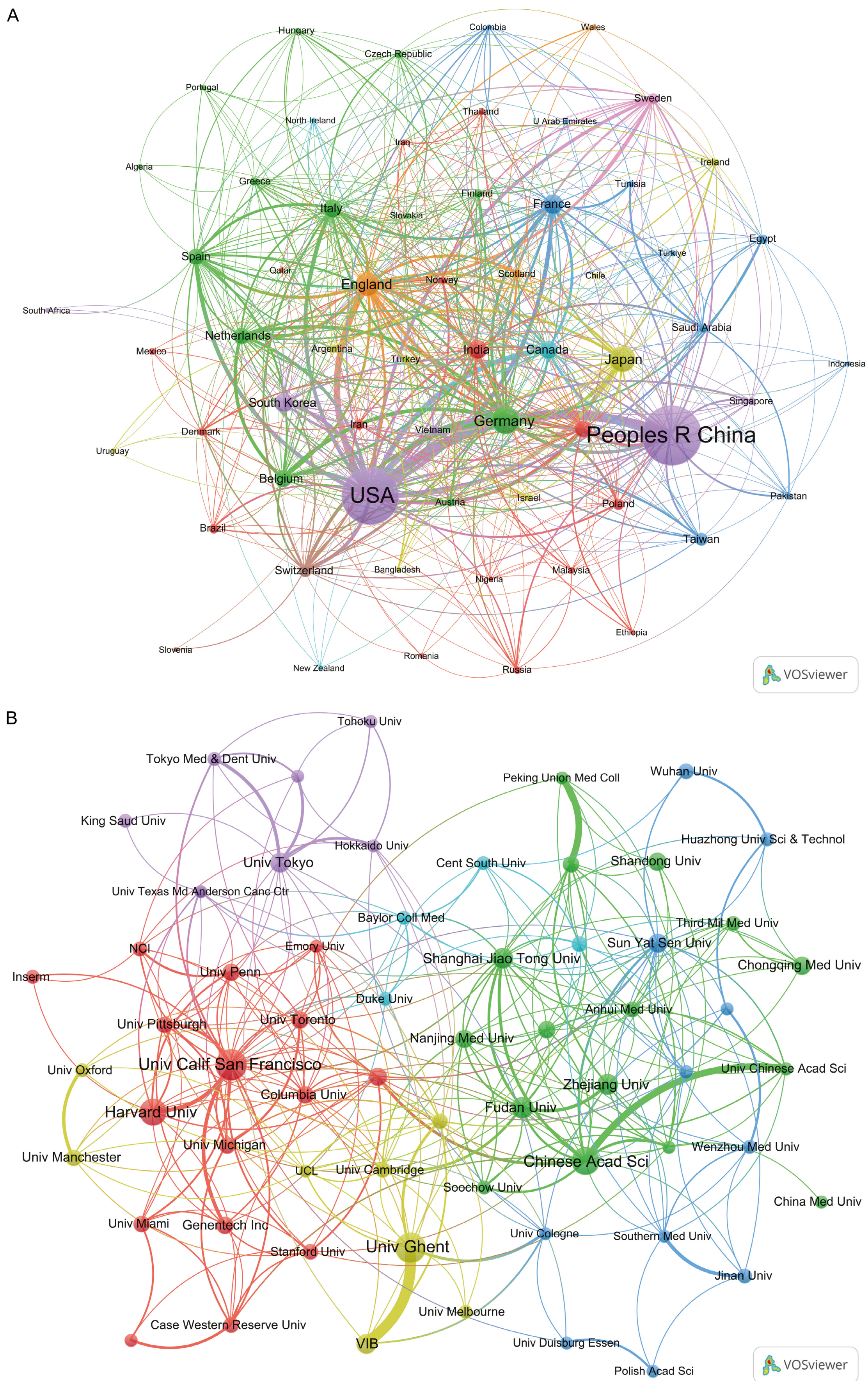
This table lists the 25 references with the strongest citation bursts in TNFAIP3/A20 research, identified through temporal citation analysis (2003-01-01 to 2025-12-31). These publications represent landmark studies that gained rapid, concentrated recognition for advancing understanding of TNFAIP3 in immunity and inflammation.

Supplementary Table 5. High-frequency keywords and thematic clusters in autoimmune and inflammatory disease contexts (2003-01-01 to 2025-12-31)

Cluster ID	Cluster Label	Representative Keywords	Mechanistic Focus
Red Cluster	Gene Expression & Cellular Responses in Disease	gene-expression, cancer, identification, cells, responses	Molecular profiling, functional genomics, and cellular behavior in disease contexts
Yellow Cluster	NF-κB Signaling, Inflammation & Cell Survival	NF-κB, inflammation, apoptosis, inhibition, TNF-α	Control of inflammatory responses, regulation of programmed cell death (apoptosis), and cytokine signaling
Green Cluster	Ubiquitin-dependent Regulation of Inflammasome and Cell Death	activation, cell-death, NLRP3 inflammasome, ubiquitination	Post-translational control (via ubiquitination) of innate immune sensor activation and its associated inflammatory cell death pathways
Blue Cluster	A20 in Disease Genetics and Risk	a20, disease, association, risk, variants, mutations	Linking genetic variations in TNFAIP3 to disease susceptibility and exploring functional consequences of coding changes

Keyword clusters were derived via co-occurrence network analysis. Each cluster aggregates mechanistic themes and disease links, reflecting the conceptual structure of A20 research. Core foci include transcriptional regulation, innate immunity, and autoinflammatory signaling.

A20 (TNFAIP3) in autoimmunity and inflammation



Supplementary Figure 2. Global research landscape of TNFAIP3 in autoimmunity and inflammation. A. Geographical distribution of publications by country, with node size representing the number of papers published by the country, the connecting line representing the countries' collaborative relationship with each other, and the width of the connecting line representing the closeness of the collaborative relationship. B. Institutional collaboration network showing research linkages between leading institutions. Visualizations generated using VOSviewer.

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