Journal of Multidisciplinary Healthcare

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Global Research Trends and Focus on the Link Between Heart Failure and NLRP3 Inflammasome: A Bibliometric Analysis From 2010 to 2024

YanJie Lian[1,2,*], Heyi Zhang[1,2,*], Wenlong Xing[1], Sinai Li[3], Xiaolei Lai[1], Sihan Jia[1], JuJu Shang[1], Hongxu Liu[1]

[1]Department of Cardiovascular, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, 100010, People's Republic of China; [2]Graduate School of Capital Medical University, Beijing, 100069, People's Republic of China; [3]Beijing Institute of Traditional Chinese Medicine, Beijing, 100010, People's Republic of China

*These authors contributed equally to this work

Correspondence: JuJu Shang, Department of cardiovascular, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, 100010, People's Republic of China, Email shangjuju@bjzhongyi.com; Hongxu Liu, Department of cardiovascular, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, 100010, People's Republic of China, Email lhx_263.net

Background: Heart failure (HF) is characterized by elevated morbidity, mortality, and rehospitalization frequencies. This condition imposes a considerable medical burden and fiscal strain on society. Inflammation plays a crucial role in the inception, advancement, and outcome of HF. Despite mounting evidence demonstrating the pivotal function of the NLRP3 inflammasome in HF, a thorough bibliometric examination of research focal points and trajectories in this domain has yet to be undertaken.

Methods: Publications related to the NLRP3 inflammasome in HF were retrieved from the Web of Science database spanning 2010–2024. The acquired data were subsequently analyzed utilizing various visualization instruments, including Citespace, VOSviewer, Scimago Graphica, and Microsoft Office Excel 2021.

Results: A total of 282 papers were included in the analysis, authored by 2,130 researchers from 500 institutions across 34 nations/regions. China emerged as a significant contributor to this field, producing the highest number of outputs. Antonio Abbate was identified as the most prolific author. Virginia Commonwealth University and Wuhan University were the institutions with the highest publication output. *INTERNATIONAL IMMUNOPHARMACOLOGY* was the periodical with the most numerous publications in this sphere. *CIRCULATION*, however, received the highest number of citations, indicating its substantial influence on investigations in this field. Contemporary research focal points primarily concentrate on the activation and inhibition pathways of the NLRP3 inflammasome, the exploration of novel HF targets, and the association between HF and mitochondrial function. Future research trajectories are likely to encompass investigations into the relationship between HF and pyroptosis, as well as clinical studies on pharmaceuticals targeting the NLRP3 inflammasome as a therapeutic approach for HF.

Conclusion: This investigation provides a comprehensive bibliometric analysis and synopsis of NLRP3 inflammable-related studies in HF. The findings offer a conceptual foundation for further research on the NLRP3 inflammasome in HF and provide valuable guidance for future research directions in this domain.

Keywords: heart failure, NLRP3, inflammasome, visualization analysis

Introduction

Heart failure(HF) is a multifaceted and life-threatening clinical syndrome characterized by significant impacts on morbidity and mortality, diminished functional capacity, reduced quality of life, and substantial economic burden.[1] The primary mechanisms underlying HF development are myocardial remodeling and fibrosis, with inflammation playing a pivotal role in these pathological processes.[2] Recent investigations have underscored the critical role of the inflammatory cascade initiated by the activation of the NLRP3 inflammasome, which functions as a signal transducer in the immune system and significantly

Received: 13 November 2024
Accepted: 21 January 2025
Published: 8 February 2025

contributes to the onset and progression of HF.[3,4] The activation of the NLRP3 inflammasome has been associated with the pathogenesis of various auto-inflammatory, autoimmune, and metabolic diseases.[5,6] This activation stimulates the expression and secretion of interleukin-1β (IL-1β), as well as interleukin-18 (IL-18), thereby initiating downstream inflammatory responses.[7] Furthermore, the NLRP3 inflammasome mediates a form of programmed cell death known as "pyroptosis".[8] Pyroptosis participates in ventricular remodeling through pathophysiological processes such as myocardial hypertrophy, fibrosis, and cell death, ultimately leading to cardiac dysfunction.[9,10] Consequently, modulation of the NLRP3 inflammasome pathway, which represents a promising therapeutic strategy for impeding HF progression.

Although research into the NLRP3 inflammasome's role in HF remains in its early stages, significant advancements have been achieved. Elevated expression of the NLRP3 inflammasome has been documented within the myocardial tissue of HF patients, which suggests a potential exacerbating effect on cardiac remodeling and dysfunction.[11,12] Blood levels of the NLRP3 inflammasome have been proposed as a biomarker for assessing HF severity and prognosis, as well as guiding therapeutic regimens in HF patients.[13] Preliminary studies investigating NLRP3 activation inhibitors, including MCC950 and colchicine, have yielded promising results in preclinical animal models.[14,15] Additionally, recent research suggests that small molecule inhibitors targeting CB1R/NLRP3 signaling may effectively mitigate cardiotoxicity induced by antipsychotic drugs.[16] In recent years, research on NLRP3 has intensified, reflecting its potential in the diagnosis as well as therapy of HF Bibliometrics, an interdisciplinary field that emerged in 1969, integrates mathematics and statistics to quantitatively analyze and visually represent literature, authors, institutions, and nations/regions.[17] In this study, we employ Citespace, VOSviewer, Scimago Graphica, as well as Microsoft Office Excel 2021 to analyze the evolving structure of network research and future research trends in NLRP3 inflammasome in HF from 2010 to the present. Our aim is to construct a scientific knowledge map of the field and provide valuable insights for subsequent investigations in this domain.

Methods

Search Strategy

The WoSCC database (https://www.webofscience.com/wos/woscc/basic-search) is widely acknowledged as an essential resource in the international academic community. In this study, the WoSCC was utilized as the target database, employing the following search strategy: (TS=(NLRP3 OR "NLRP3 inflammasome" OR "NOD-like receptor thermal protein domain associated protein 3" OR "Nod-like receptor protein 3 inflammasome" OR "NLR Family Pyrin Domain Containing 3 Protein")) AND TS=("heart failure" OR HF OR "Ischemic heart failure" OR "Cardiac Failure" OR "Heart Decompensation" OR "Myocardial Failure" OR "Congestive Heart Failure" OR "Left Sided Heart Failure" OR "Right Sided Heart Failure"). The search was confined to the period from 2010–01-01 to 2024-2-28, yielding 461 literature records. Subsequently, the literature types were filtered to include only "Article" and "Review Article", resulting in 315 English-language records. Following a meticulous screening process conducted by the researchers, 33 irrelevant articles were excluded, leaving a final dataset of 282 valid articles (Figure 1). The collected literature records were downloaded and preserved in a plain text file, formatted as "complete records and cited references", to serve as a sample for data analysis. Additionally, original data pertaining to publication country/region information, institutions, journals, authors, and article types were collected and statistically analyzed using Microsoft Excel.

Data Assessment

Bibliometric assessment was performed using two specialized software packages: VOSviewer v.1.6.20 (https://www.vosviewer.com/) and CiteSpace 6.3.R1 (http://cluster.cis.drexel.edu/~cchen/citespace/). VOSviewer was employed to process and analyze the acquired data, generating maps where different nodes represent elements, including nations, organizations, as well as authors. These nodes' sizes indicate the frequency or significance of these elements within the dataset. CiteSpace was utilized to construct visual representations of top-level reference bursts, keyword bursts, as well as keyword time zone maps. These visualizations served to elucidate research hotspots across different periods and to identify future research trends. Furthermore, Scimago Graphica V1.0.25 (https://graphica.app/) was employed for generating a geographic distribution map of publications focusing on NLRP3 inflammasome in heart failure. Microsoft Office Excel 2021 was utilized for chart creation and additional data visualization.

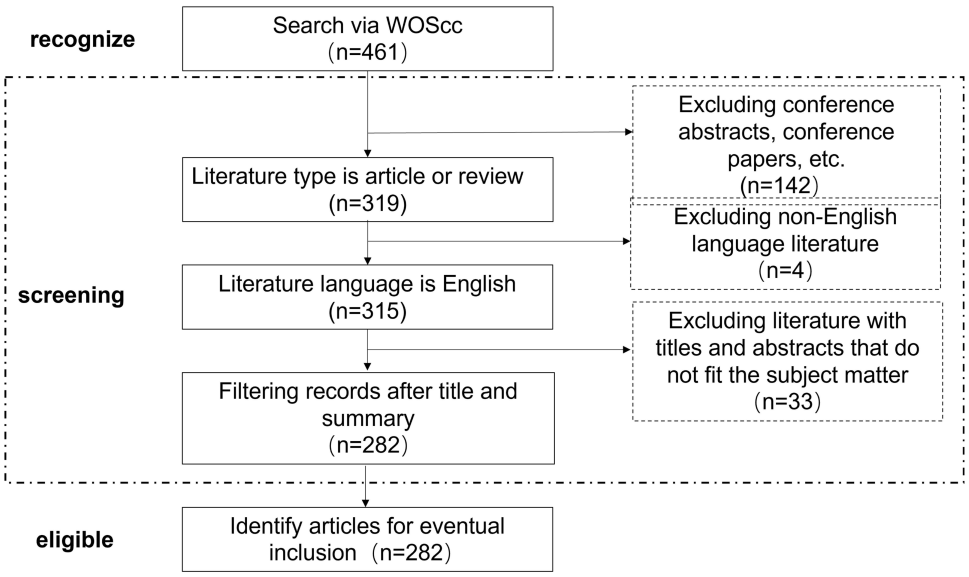

Figure 1 Flowchart of Literature Screening.

Result

Quantitative Assessment of Publications

The corpus of 282 papers analyzed in this research originated from 500 organizations across 34 nations, authored by 2,130 researchers, and disseminated in 133 journals. The publications have garnered 20,180 citations out of 2,465 journals. The annual research output is illustrated in Figure 2. Overall, the annual publication rate in this field has exhibited steady and rapid growth. Prior to 2011, research on NLRP3 inflammasome in heart failure had not been initiated. The period from 2011 to 2016 was characterized by a relatively low number of publications, indicating an early stage of research in this domain. However, from 2017 onwards, a marked increase in the quantity of publications has been observed. This trend suggests that NLRP3 inflammasome has garnered more and more attention from academics in recent decades, emerging as a novel focal point in heart failure research.

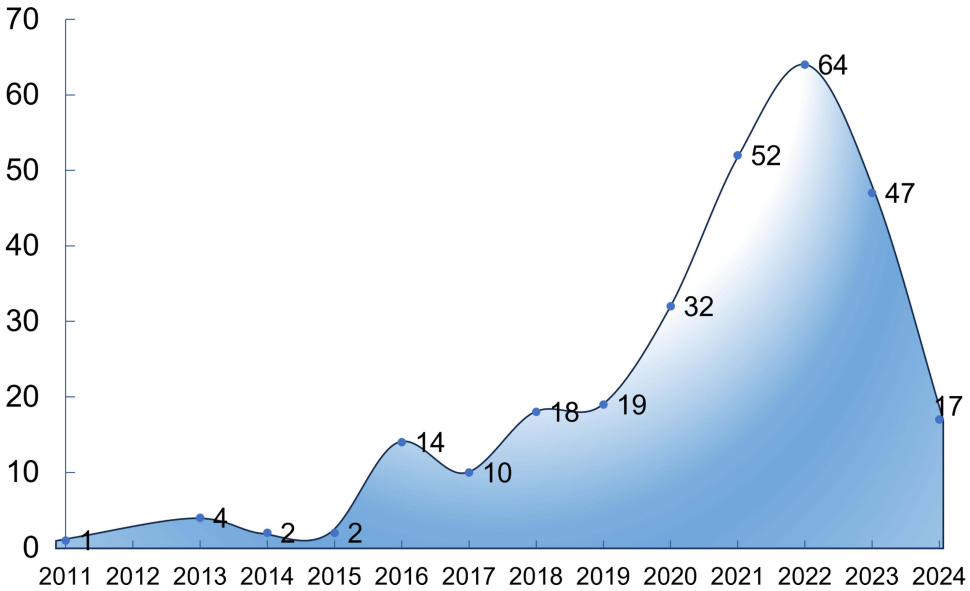

Figure 2 Trends in the growth of publications.

https://doi.org/10.2147/JMDH.S505356

Journal and Co-Cited Journal Analysis

Figure 3A presents the top 15 journals with the highest productivity in NLRP3 inflammasome research related to HF, providing valuable guidance for researchers considering manuscript submissions. Among these publications, *INTERNATIONAL IMMUNOPHARMACOLOGY* emerged as the most prolific, publishing 11 papers. *BIOMEDICINE & PHARMACOTHERAPY, CARDIOVASCULAR RESEARCH, CIRCULATION RESEARCH*, and *JOURNAL OF CARDIOVASCULAR PHARMACOLOGY* each contributed 6 publications. Within the top 15 journals, *CIRCULATION* boasted the highest impact factor (IF=35.5, 2024), followed by *BIOMEDICINE & PHARMACOTHERAPY* (IF=6.9, 2024). Of the 15 most frequently co-cited journals, four were cited over 150 times. CIRCULATION received the highest number of citations (199), followed closely by *CIRCULATION RESEARCH* (181 citations) and *CARDIOVASCULAR RESEARCH* (152 citations) (Figure 3B). An analysis of the overlapping journals in both figures (Figure 4) suggests that this field encompasses research spanning clinical medicine, immunology, and molecular biology.

Scientific Cooperation

To identify the nations making the most significant contributions to this research area, 500 organizations across 34 nations/regions were analyzed. Figure 5A and B illustrate the geographical distribution of the total number of articles and visualize collaborative networks. The top10 nations with the greatest publication output are distributed across North America, Asia, and

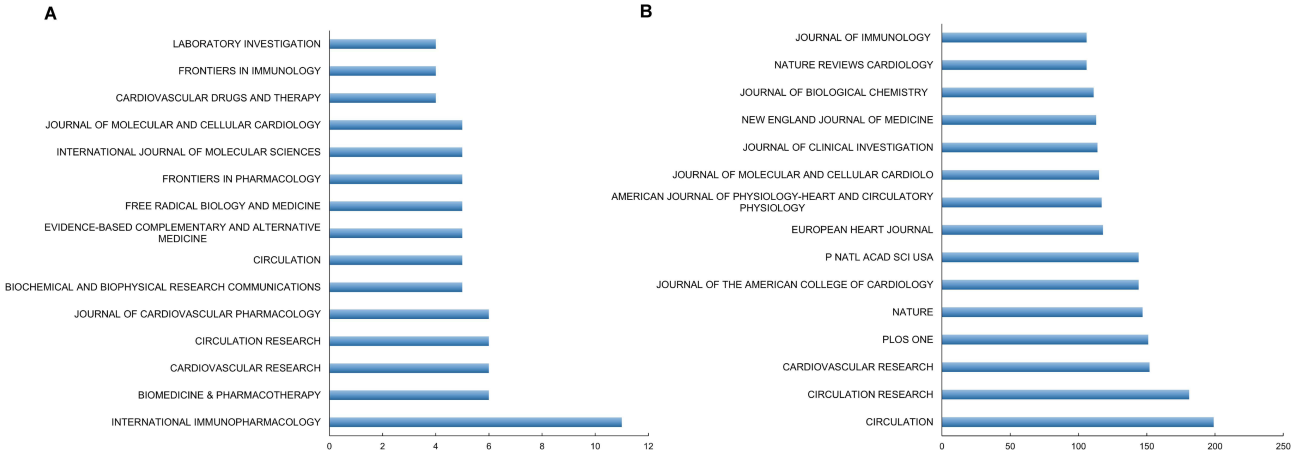

Figure 3 (**A**) Top 15 journals in NLRP3 inflammasome research related to HF. (**B**) The 15 most co-cited journals in NLRP3 inflammasome and HF research.

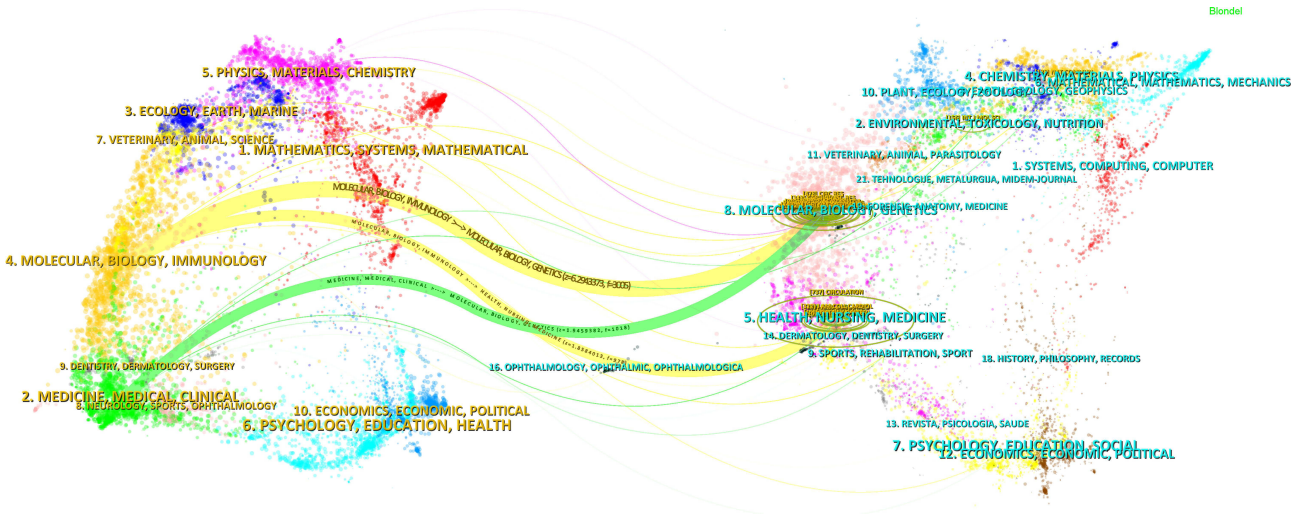

Figure 4 Journal overlay map of NLRP3 inflammasome research in HF.

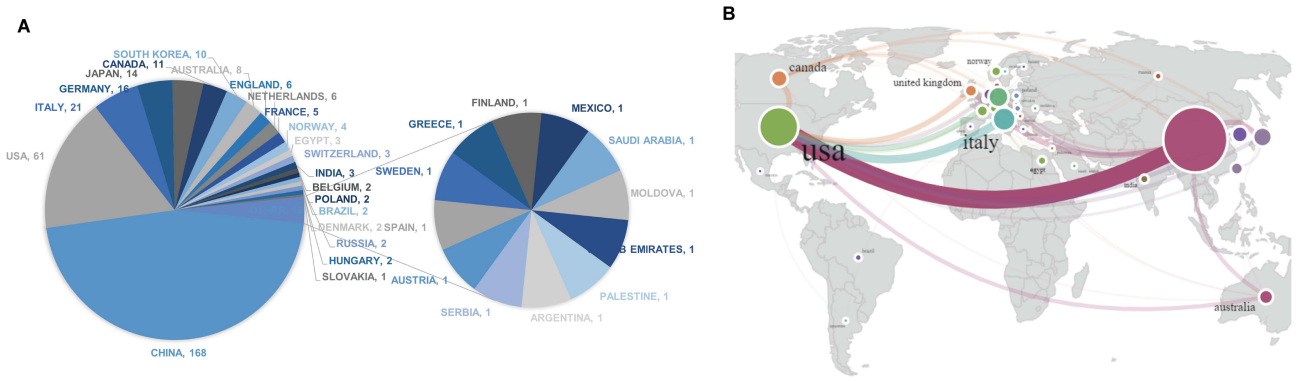

Figure 5 (**A**) Global publication output related to NLRP3 inflammasome research in HF. (**B**) Worldwide distribution of NLRP3 inflammasome research in HF based on publication data.

Europe, with China, the United States of America, Italy, Germany, and Japan comprising the top five, respectively. Notably, North American and European nations (USA, Canada, Netherlands, etc). and Japan demonstrate higher average citations per publication, while Asian nations, particularly China, show slightly lower citation rates (Table 1).

Analysis of Institutions

Table 2 presents the top 11 institutions based on their contributions to NLRP3 inflammasome research in HF. These institutions are distributed across China (8), Germany (2), and the United States. Virginia Commonwealth University and Wuhan University share the highest publication count with 14 articles each, followed closely by Harbin Medical University (10) and Fudan University (8). In terms of Total Link Strength (TLS), Virginia Commonwealth University leads with 1074, followed by the University of Queensland (696) and Temple University (528). The data reveals substantial collaboration among these institutions.

Author/Institutional Cooperation

The visualization of scientific collaboration in the author and institutional dimensions reveals a high degree of interconnectedness, as evidenced by the substantial number of nodes and the intricate network of connections depicted in Figure 6. In the field of NLRP3 inflammasome research related to heart failure, Abbate, Antonio, Toldo, Stefano, and Bonaventura, Aldo have emerged as leading contributors, based on their publication volume (Figure 6A). The research findings of these authors have played a fundamental role to explore the significance of the NLRP3 inflammasome in the context of heart failure. The institutional collaboration network, illustrated in Figure 6B, highlights Virginia Commonwealth University, Wuhan

Table 1 Influential Nations/Regions in NLRP3 Inflammasome Research Related to HF

Rank	Country	Total number of publications	Total number of citations
1	China	168	3122
2	The United States	61	3105
3	Italy	21	536
4	Germany	16	530
5	Japan	14	767
6	Canada	11	610
7	South Korea	10	419
8	Australia	8	747
9	Netherlands	6	344
10	United kingdom	6	120

https://doi.org/10.2147/JMDH.S505356

Table 2 Influential Institutions in NLRP3 Inflammasome Research Related to HF

Rank	Organization	Country	Total number of publications	Organization	Country	Total number of citations
1	Virginia Commonwealth University	USA	14	Virginia Commonwealth University	USA	1074
2	Wuhan University	China	14	University of Queensland	Australia	696
3	Harbin Medical University	China	10	Temple University	USA	528
4	Fudan University	China	8	Harbin Medical University	China	316
5	Charite University Med Berlin	Germany	6	University of Alberta	Canada	278
6	Chongqing med University	China	6	Sun Yat-sen University	China	254
7	DZHK German Ctr Cardiovasc Res	Germany	6	Fudan University	China	242
8	Hubei Key Laboratory of heart	China	6	Harvard Medical School	USA	223
9	Nanjing Medical University	China	6	University of California, San Diego	USA	205
10	Shanghai JiaoTong University	China	6	Nanjing Medical University	China	186
11	Xi An Jiao Tong University	China	6	University of Naples Federico II	Italy	175

University, and Harbin Medical University as the most prominent nodes, indicating their substantial contributions to this research area.

Keywords Analysis

Keywords serve as indicators of the core content and themes within the literature. Through a comprehensive analysis of frequently occurring keywords, a deeper understanding of relevant research directions and focal points in the field can be obtained. A thorough examination of 282 papers using CiteSpace yielded a total of 1221 keywords. The ten most frequently occurring keywords, in descending order of frequency, were identified as follows: nlrp3 inflammasomes (144), heart failure (130), activation (71), oxidative stress (45), injury (42), myocardial infarction (35), expression (33), dysfunction (29), apoptosis (28), and fibrosis (26) (Figure 7A).

Keyword clustering analysis was employed to elucidate the distribution of core content and categorize keywords based on their similarity.[18] The CiteSpace keyword clustering and hotspot identification map, presented in Figure 7B, revealed ten distinct research hotspots: "#0: cardiac remodeling", "#1: angiotensin ii", "#2: cardiovascular diseases", "#3: cardiac dysfunction", "#4: heart failure", "#5: health", "#6: prmt5", "#7: nf-kappa b", "#8: cognitive impairment", and "#9: diabetic cardiomyopathy". Table 3 provides a detailed characterization of each cluster depicted in Figure 7B,

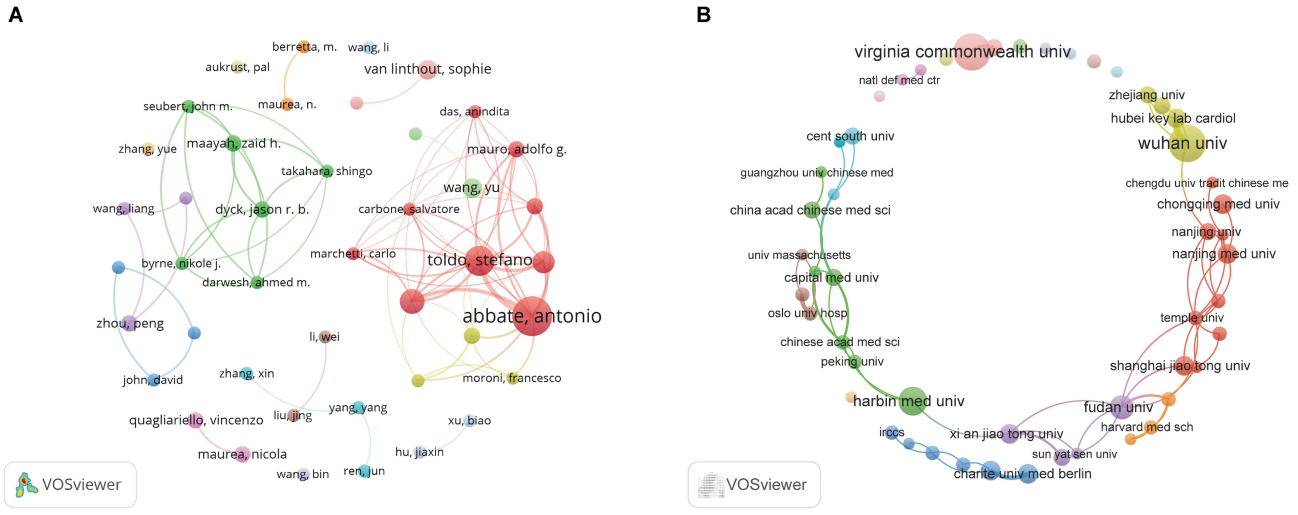

Figure 6 (**A**) Cooperation network of authors. (**B**) Visualization of organizations correlated with NLRP3 inflammasome within HF publications.

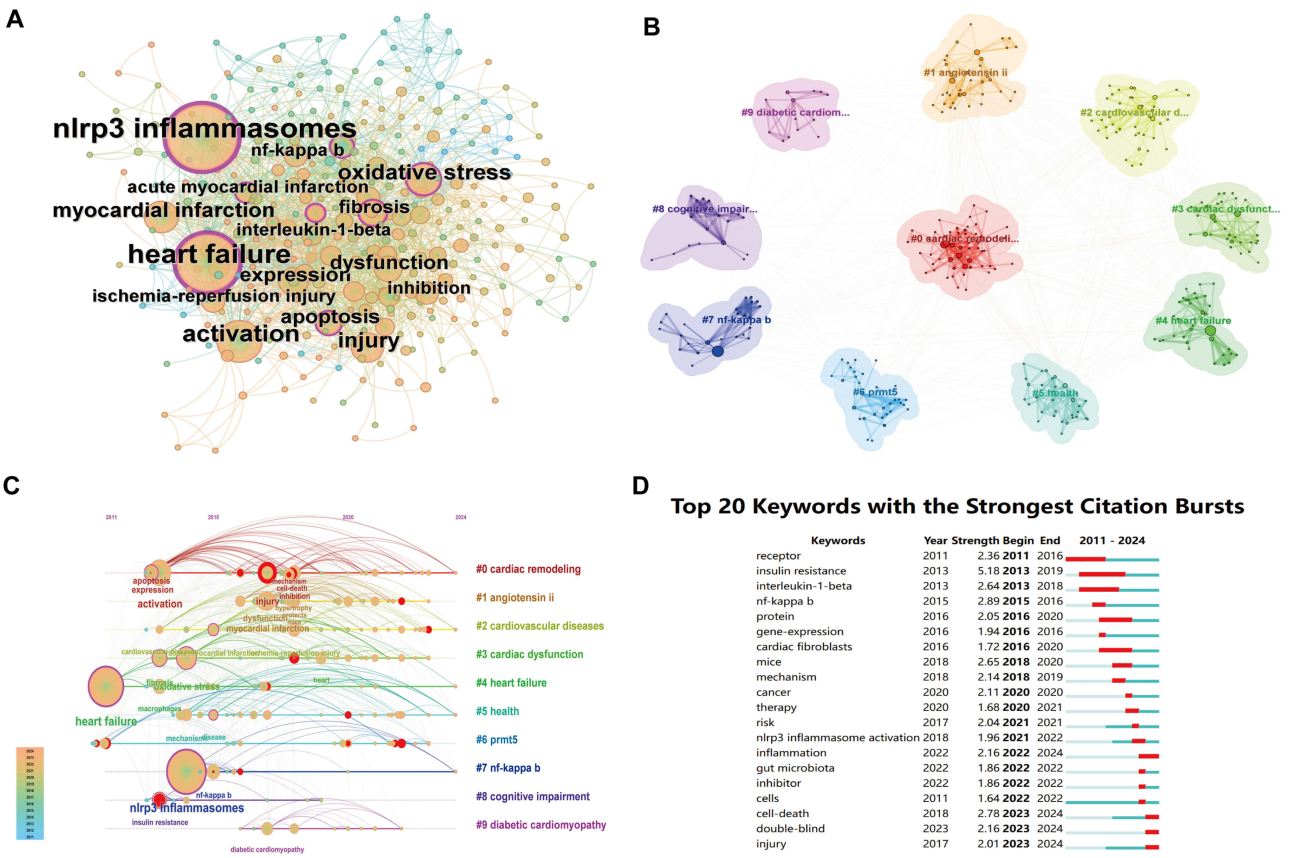

Figure 7 (**A**) High-frequency keywords. (**B**) Cluster diagram of keywords. (**C**) Timeline diagram of keywords. (**D**) Top 20 keywords with the strongest citation bursts (blue line indicates the timeline, and the red segments indicate the time period in which the keywords were highlighted).

encompassing cluster number, cluster label, average publication year of the clustered literature, research focus of the clustered literature, and the number of cluster members. The keyword timeline view was utilized to track the evolution of keywords over time, offering a visual representation of the duration and historical progression of each cluster. Notably, as illustrated in Figure 7C, the most recent and dynamically active clusters identified in the analysis were cluster #0 ("cardiac remodeling"), cluster #2 ("cardiovascular diseases"), cluster #4 ("heart failure"), cluster #5 ("health"), and cluster #7 ("nf-kappa b"). This observation suggests a growing research interest in these specific areas.

Table 3 Keyword Clustering Features

Cluster ID	Size	Silhouette	Mean (Year)	Top Terms
0	57	0.609	2019	cardiac remodeling; obesity; oxidative stress; pyroptosis; atrial natriuretic peptide
1	42	0.707	2019	angiotensin ii; pressure overload; ventricular remodeling; mcc950; myocardial hypertrophy
2	42	0.743	2019	cardiovascular diseases; pericarditis; tumor necrosis factor; recurrent pericarditis; ischemia/reperfusion injury
3	39	0.526	2019	cardiac dysfunction; reactive oxygen species; mitochondrial dysfunction; heart; catecholamines
4	34	0.764	2016	heart failure; risk; liver disease; anakinra; ventricular arrhythmia
5	34	0.783	2019	health; prevention; purinergic p2x7; cardiac; aim2 inflammasome
6	33	0.716	2018	prmt5; inflammatory injury; left ventricle; isoliquiritigenin
7	25	0.848	2017	nf-kappa b; cardiac fibroblasts; nlrp3 inflammasome; nf-kappa b p65; hirudin
8	21	0.874	2014	cognitive impairment; sex-differences; toll-like receptor (tlr)-4; amyloidogenesis; apnea-hypopnea
9	13	0.916	2019	diabetic cardiomyopathy; fndc5; atorvastatin; metformin; ampk alpha

https://doi.org/10.2147/JMDH.S505356

Keyword prominence, which refers to the sudden surge in the frequency of keyword appearances at specific time points, was analyzed to identify emerging research frontiers. Keywords exhibiting high rates of frequency change were detected at corresponding time nodes, and a keyword prominence year distribution map was generated to analyze current research hotspots and frontiers. Figure 7D presents an analysis of the top 20 emergent keywords from 2011 to 2024. Keywords demonstrating increased intensity of recent outbreaks and high intensity (≥2) include "inflammation", "cell-death", "double-blind", and "injury".

Cluster Assessment of Co-Cited Literature

Co-cited literature means pairs of articles that are simultaneously cited, with co-citation frequency determined through quantitative analysis[18]. Citation counts serve as a metric for evaluating the impact as well as scholarly value of research, while thematic clustering of co-cited literature elucidates the primary research focus and historical development within a specific field.[19] The most frequently co-cited publication was authored by Toldo, Stefano, entitled "The NLRP3 inflammasome in acute myocardial infarction", and published in Nature Reviews Cardiology. This was followed by an article titled "Anti-inflammatory therapy with canakinumab for atherosclerotic disease". Notably, among the top 10 cited articles, three emphasized the NLRP3 inflammasome as a therapeutic target for cardiovascular disease, while two focused on the NLRP3 inflammasome inhibitor MCC950.

The co-citation network analysis identified 12 distinct clusters, characterized by significant modularity (Q=0.7216) and high silhouette scores (S=0.8989), indicating robust cluster credibility and uniqueness[19] (Figure 8). Based on the co-citation relationships, the current research themes surrounding the NLRP3 inflammasome in HF can be summarized as follows: 1. Etiology of HF: Clusters 0, 2, and 3 concentrated on various pathways leading to HF, including myocardial infarction and atrial fibrillation. 2. Pathologic features of HF onset: Clusters 1, 4, and 7 focused on elucidating the mechanisms by which the NLRP3 inflammasome contributes to HF pathogenesis. Clusters 8 and 10 highlighted the influence of mitochondrial function on NLRP3 inflammasome activity. 3. Therapeutic interventions and targets for HF: Clusters 5 and 6 explored the mechanisms of action of drugs that treat HF through NLRP3 inflammasome inhibition. Cluster 11 was dedicated to investigating novel therapeutic targets for HF management.

Discussion

In this study, VOSviewer and CiteSpace were employed to carry out bibliometric mapping as well as visualization of 282 relevant research papers extracted out of the Web of Science core collection. A systematic assessment of the current status of NLRP3 inflammasome research within HF as well as potential research directions in the future has been undertaken. To the best of our knowledge, this represents the first comprehensive bibliometric analysis focusing on the NLRP3 inflammasome in HF. Quantitative, qualitative, and integrative analyses were utilized to identify research trends and shifts, which are elaborated upon in the following sections, providing a comprehensive overview of our findings.

Analysis of Basic Content

As illustrated in Figure 1, the number of publications has exhibited slight fluctuations since the first relevant publication in 2010. However, a general upward trend has been maintained, with the peak number of publications occurring in 2023. This trajectory suggests that the field has gradually entered a mature stage of development over time. The top three nations in terms of publication output are China, the United States, and Italy. Notably, eight of the top eleven organizations publishing the most relevant research are located in China. Nevertheless, the mean citation rate of these articles is comparatively low, suggesting that the overall quality of Chinese publications in this field may necessitate enhancement. Institutions with higher citation rates are predominantly situated in the United States. Furthermore, the top ten most prolific authors in this field are primarily from the United States and China. These findings underscore that China and the United States are at the forefront of research in this domain, while also highlighting disparities in the development of individual nations and regions within this field. It is noteworthy that China entered this research arena in 2013 and has since ascended to the top rank in terms of total publications. This rapid progress demonstrates China's substantial contribution to research in this field over the past decade.

Emerging Topics

By combining high-frequency keywords, keyword clustering, and co-cited literature clustering analyses, the research hotspots can be summarized as follows:

Inhibition and Activation of NLRP3 Inflammasome

The NLRP3 inflammasome has been identified as a crucial factor in cardiovascular diseases, with its inhibition emerging as a promising therapeutic approach. Selective NLRP3 inflammasome inhibitors, such as MCC950 and INF4E, have demonstrated efficacy in attenuating cardiac inflammation and associated pathologies. MCC950, in particular, has been observed to diminish the expression of collagen type I (COL1), collagen type III (COL3), as well as alpha-smooth muscle actin (α-SMA), thereby enhancing cardiac metabolism and mitigating HF induced by pressure overload. This compound has also been shown to effectively inhibit myocardial remodeling in murine models following transverse aortic constriction (TAC) surgery.[20] INF4E has been found to activate the pro-survival risk pathway, leading to improved mitochondrial function and prevention of ischemia/reperfusion (I/R)-induced myocardial injury and dysfunction.[21] These findings underscore the potential of NLRP3 inflammasome-targeted therapies in the management of HF and related cardiovascular conditions. Colchicine has been observed to upregulate SIRT2 expression, resulting in the inactivation of the NLRP3 inflammasome through NLRP3 deacetylation.[22] However, further research is required to determine whether its role in cardiovascular disease is mediated by effects on NLRP3 inflammasome and/or IL-1 signaling.[23] Resveratrol has been shown to inhibit NLRP3 inflammasome activity, reduce TGF-β1 production, and downregulate p-SMAD2/SMAD2 expression in the heart, leading to improved cardiac function and reduced myocardial fibrosis.[24] Muscarinone has been found to exert a beneficial effect on cardiac function in mice post-myocardial infarction by suppressing chronic inflammation mediated by cardiac macrophages. This effect is achieved via the suppression of the NF-κB pathway as well as the NLRP3 inflammasome, which are key drivers of inflammatory responses in cardiovascular disease.[25] MicroRNA-495 has been observed to ameliorate cardiac microvascular endothelial cell injury and inflammatory responses through inhibition of the NLRP3 inflammasome signaling pathway.[26] Activation of the NLRP3 inflammasome has been shown to promote myocardial inflammation and contractile dysfunction

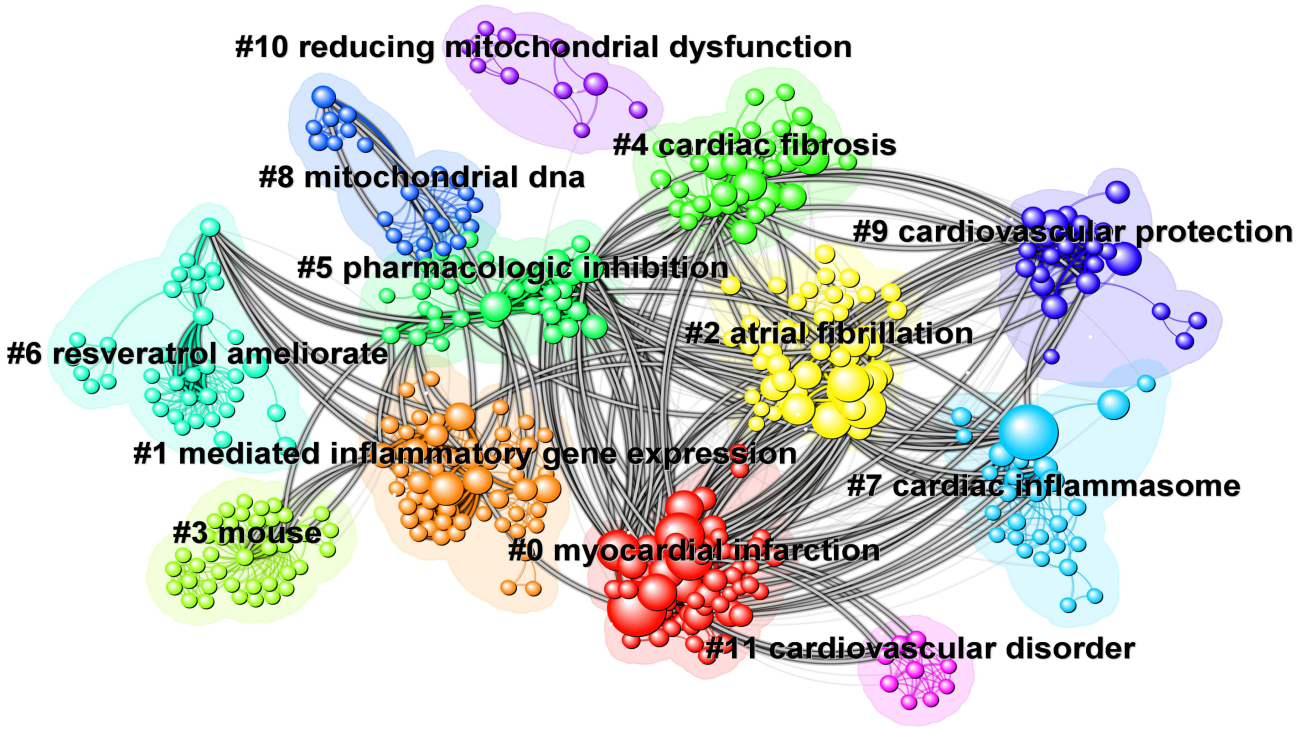

Figure 8 Literature co-citation cluster mapping.

https://doi.org/10.2147/JMDH.S505356

through the production of proinflammatory IL-1.[27] Notably, blockade of IL-1β signaling with IL-1 receptor antagonists has been found to reverse these phenotypes, suggesting a potential therapeutic approach for the treatment of HF.

NLRP3 inflammasome-mediated thermoprotein deposition has been observed to exacerbate pressure overload-induced cardiac hypertrophy, fibrosis, as well as dysfunction in mice.[28] Exposure to silicon dioxide nanoparticles (SiNPs) has been demonstrated to induce thermoprotein deposition as well as cardiac hypertrophy through the ROS/NLRP3/Caspase-1 pathway,[29] leading to adverse cardiovascular effects including focal death and cardiac hypertrophy. Cardiac glycosides, such as digoxin, a Na+/K+-ATPase inhibitor widely used in the treatment of HF and arrhythmias, have been associated with increased mortality. Motoi Kobayashi et al have demonstrated that the cardiac glycoside ouabain promotes cardiac inflammation and dysfunction through activation of the NLRP3 inflammasome as well as release of IL-1β from macrophages.[30] This finding provides new insights into the underlying mechanisms of adverse effects associated with cardiac glycosides.

Exploring Novel Targets for Heart Failure Therapy

Protein arginine methyltransferase 5 (PRMT5), a methyltransferase catalyzing the formation of methylated residues on histones and non-histone proteins, has emerged as a promising therapeutic target for various diseases, including infectious diseases, cardiac disorders, and malignancies.[31] Cheng et al demonstrated that PRMT5 plays a crucial role in regulating cardiac hypertrophic signaling, suggesting that the upregulation of PRMT5 expression in cardiac tissue may serve as a potential therapeutic strategy for preventing myocardial hypertrophy and HF.[32]

G protein-coupled receptor kinases (GRKs) constitute a family of kinases associated with rapid desensitization of G protein-coupled receptors. Among these, GRK2 was the first to be linked to the cardiovascular system, participating in various pathophysiological processes such as oxidative stress and cellular fibrosis.[33,34] Elevated GRK2 expression and activity have been implicated in adverse cardiac remodeling.[35] Research has shown that GRK2 activity is upregulated during HF and hypertrophy,[36] positioning GRK2 as a potential target for novel investigational drugs aimed at treating cardiac dysfunction in HF.[37] The GRK2 inhibitor paroxetine has been found to support cardiac function and inhibit cardiac remodeling by attenuating GRK2 activity in cardiac hypertrophy.[38] Furthermore, GRK2 has been shown to regulate NLRP3 inflammasomes in isoproterenol (ISO)-induced cardiac hypertrophy. In HF treatment, pretreatment with GRK2 siRNA or paroxetine, followed by ISO exposure, resulted in decreased protein levels of NLRP3, ASC, caspase-1, and NLRP3.[39]

Targeting the Therapeutic Potential of NLRP3 Inflammasome and Mitochondria in Heart Failure

Pathological myocardial hypertrophy, a major risk factor for cardiovascular disease progression,[40] can lead to hypertension, myocardial fibrosis, HF, and ultimately, death from cardiac-related causes. Mitochondrial dysfunction has been identified as a potential key mechanism and a prominent feature in the process of myocardial hypertrophy.[41] Mounting evidence suggests that the activation of the NLRP3 inflammasome is intricately linked to mitochondrial dysfunction. In the context of HF, the contribution of fatty acids to ATP production is diminished, while alternative metabolic pathways, including glycolysis, are upregulated to compensate for the reduced energy yield.[42] This process, known as metabolic reprogramming, is accompanied by alterations in genes encoding proteins associated with mitochondrial function.[43] When mitochondrial activity is dysregulated through voltage-dependent inhibition of anion channels, both reactive oxygen species (ROS) production and inflammatory vesicle activation are suppressed.[44] Li et al[45] revealed that the dysregulation of mitochondrial homeostasis can precipitate excessive ROS generation, which in turn activates the NLRP3 inflammasome, thereby accelerating the progression towards HF. Another study demonstrated that NLRP3 inflammasome activation contributes to angiotensin II (Ang II)-induced cardiomyopathy through mitochondrial dysfunction, inflammation, oxidative stress, and fibrosis.[46] Notably, NLRP3 knockout was found to mitigate these effects, suggesting that targeting NLRP3 or mitochondria could be a promising therapeutic approach for Ang II-related cardiac conditions. These findings underscore the intricate association involving mitochondrial dynamics as well as NLRP3 inflammasome activation, opening up novel avenues for research that explore the interplay between NLRP3 inflammasome signaling, mitochondrial function, and myocardial hypertrophy.

Future Research Priorities

Relationship Between Cellular Pyroptosis and Heart Failure

The formation of NLRP3 inflammasomes in cardiomyocytes has been demonstrated to possess the capability of activating caspase-1 and inducing cellular pyroptosis,[47] Cheng et al[48] were the first to elucidate that cardiomyocyte pyroptosis, triggered by NLRP3 inflammasome activation via caspase-1, can contribute to the progression of myocardial dysfunction. In a subsequent study, Zhang et al[49] revealed that BMP-2 exhibits inhibitory effects on NLRP3 inflammasome activation and cellular pyroptosis, suggesting its potential as a novel therapeutic target for HF. The exploration of the intricate relationship between pyroptosis and HF in future research endeavors may facilitate the development of strategies aimed at decelerating the deterioration of cardiac function in HF patients.

Clinical Studies Focusing on Therapeutic Efficacy

Colchicine, a non-selective NLRP3 inflammasome inhibitor, has been utilized for decades in the prevention of acute inflammatory attacks associated with gout and familial Mediterranean fever. Recent clinical trials have demonstrated its potential efficacy in various cardiovascular diseases,[50] and its application in HF therapy is being progressively investigated.[51,52] Dapansutrile, a selective NLRP3 inflammasome inhibitor, reduces the maturation and release of IL-1β by impeding the assembly and activation of the NLRP3 inflammasome. A phase 1B, randomized, double-blind clinical study conducted by George F Wohlford et al demonstrated that a 14-day treatment regimen with Dapansutrile was well-tolerated and safe in stable NYHA class II–III patients with systolic HF.[53] Anakinra, an IL-1 receptor antagonist, indirectly modulates the downstream effects of the NLRP3 inflammasome by blocking IL-1β signaling. A double-blind, randomized, placebo-controlled, crossover trial revealed that Anakinra administration to patients with stable chronic systolic HF resulted in significant reductions in circulating CRP and IL-6 levels.[54] Furthermore, a Phase II clinical trial yielded promising data for recombinant Anakinra in patients with ST-segment elevation acute myocardial infarction or HF with reduced ejection fraction.[55] Currently, Van Tassell BW et al[56] are conducting a larger 24-week post-discharge clinical trial of Anakinra (the REDHART2 study), with anticipated positive outcomes. The development of inhibitors targeting the NLRP3 inflammasome or its downstream pathways paves the way for testing the hypothesis that NLRP3 inflammasome inhibition may improve clinical outcomes in HF patients.

The Interplay Involving Mitochondrial Dysfunction as Well as NLRP3 Inflammasome in Heart Failure

Mitochondrial dysfunction, in addition to inflammation, has been recognized as a major contributor to and plays a pathogenic role in HF.[57] Impaired mitochondrial function and autophagy can lead to increased ROS generation and cytosolic accumulation of dysfunctional mitochondria or mitochondrial DNA (mtDNA) leakage, which are potent activators of the NLRP3 inflammasome.[58,59] For instance, ischemic heart failure, a prevalent cause of HF, involves the release of damage-associated molecular patterns (DAMPs), including mitochondrial DNA and ATP, during myocardial ischemia. These DAMPs activate the NLRP3 inflammasome, subsequently triggering an inflammatory cascade. Consequently, the potential convergence of mitochondrial dysfunction as well as NLRP3 inflammasome activation is an emerging frontier in the therapeutic landscape of HF, with significant implications for the development of novel therapeutic strategies targeting these interconnected pathways.[60]

Summarization

A comprehensive analysis reveals the pivotal role of the NLRP3 inflammasome in HF development, with publications on this topic exhibiting a consistent annual increase. China and the United States have emerged as the primary contributors to this research domain. Among the institutions publishing in this field, Abbate, Antonio, and Toldo, Stefano have produced the highest number of papers. The inhibition and activation of the NLRP3 inflammasome represent current research focal points. The NLRP3 inflammasome has been demonstrated to impede myocardial remodeling and decelerate HF progression through the regulation of inflammatory responses, mitochondrial function, and fibroblast differentiation, among other pathways. NLRP3 inflammasome-mediated cellular pyroptosis in relation to HF constitutes a frontier in research. Furthermore, investigators are dedicating efforts to exploring the NLRP3 inflammasome as a target for HF drug intervention and novel therapeutic approaches. NLRP3 inflammasome inhibitors and certain anti-inflammatory agents have been shown to suppress NLRP3 inflammasome activity. Consequently, clinical research investigating the efficacy of these drugs may emerge as a key research direction in the future. As scientific advancements continue, NLRP3 inflammasome-targeted drug therapy is

anticipated to provide innovative approaches for HF diagnosis and treatment. It is noteworthy that this research field has witnessed significant contributions from various institutions and researchers. The ongoing exploration of NLRP3 inflammasome's role in HF and the development of targeted therapies underscore the potential for groundbreaking discoveries in cardiac medicine. As the scientific community delves deeper into this area, it is expected that NLRP3 inflammasome-targeted interventions will offer new perspectives and strategies for addressing the complex challenges posed by HF.

Acknowledgment

This paper has been uploaded to Authorea as a preprint: https://yvm2020.authorea.com/doi/full/10.22541/au.173096584.42119923/v1

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

National Natural Science Foundation of China:Exploring the perioperative myocardial protection mechanism of PCI by Yiqi and Blood Stasis Method based on miR-24/NF-κB/GSDMD Inflammatory Scorch Death Pathway (82174315); Regulation of PAD4/NLRP3-NETosis by Yi Qi and Blood Stasis Formula inhibits neutrophil reverse migration to prevent myocardial remodeling in ischemic heart failure (82205098); Beijing Medical Center Talent Training Program: Myocardial protection study of miR146a/TLR4/NF-κB feedback loop intervention in IHF by regulating miR146a/TLR4/NF-κB with the method of benefiting qi and expelling blood stasis (QML20221003).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Savarese G, Becher PM, Lund LH, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology[J]. *Cardiovasc Res*. 2023;118(17):3272–3287. doi:10.1093/cvr/cvac013
2. Verma SK, Krishnamurthy P, Barefield D, et al. Interleukin-10 treatment attenuates pressure overload-induced hypertrophic remodeling and improves heart function via signal transducers and activators of transcription 3-dependent inhibition of nuclear factor-kappaB[J]. *Circulation*. 2012;126(4):418~429. doi:10.1161/CIRCULATIONAHA.112.112185
3. Chen PF, Li X. NLRP3 inflammasome in atherosclerosis: mechanisms and targeted therapies[J]. *Front Pharmacol*. 2024;15:1430236. doi:10.3389/fphar.2024.1430236
4. Zhou WY, Chen CY, Chen ZH, et al. NLRP3: a Novel Mediator in Cardiovascular Disease[J]. *J Immunol Res*. 2018;2018:5702103. doi:10.1155/2018/5702103
5. Jo EK, Kim JK, Shin DM, et al. Molecular mechanisms regulating NLRP3 inflammasome activation[J]. *Cell mol Immunol*. 2016;13(2):148~159. doi:10.1038/cmi.2015.95
6. Grebe A, Hoss F, Latz E. NLRP3 Inflammasome and the IL-1 Pathway in Atherosclerosis[J]. *Circ Res*. 2018;122(12):1722~1740. doi:10.1161/CIRCRESAHA.118.311362
7. He Y, Hara H, Núñez G. Mechanism and Regulation of NLRP3 Inflammasome Activation[J]. *Trends Biochem Sci*. 2016;41(12):1012~1021. doi:10.1016/j.tibs.2016.09.002
8. Kayagaki N, Stowe IB, Lee BL, et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling[J]. *Nature*. 2015;526(7575):666~671. doi:10.1038/nature15541
9. Liu DL, Zeng X, Li X, et al. Role of NLRP3 inflammasome in the pathogenesis of cardiovascular diseases[J]. *Basic Res Cardiol*. 2018;113(1):5. doi:10.1007/s00395-017-0663-9
10. Zhang J, Huang LL, Shi X, et al. Metformin protects against myocardial ischemia-reperfusion injury and cell pyroptosis via AMPK/NLRP3 inflammasome pathway[J]. *Aging*. 2020;12(23):24270~24287. doi:10.18632/aging.202143
11. Suetomi T, Willeford A, Brand CS, et al. Inflammation and NLRP3 Inflammasome Activation Initiated in Response to Pressure Overload by Ca(2+)/Calmodulin-Dependent Protein Kinase II delta Signaling in Cardiomyocytes Are Essential for Adverse Cardiac Remodeling[J]. *Circulation*. 2018;138(22):2530~2544. doi:10.1161/CIRCULATIONAHA.118.034621

12. Wang YC, Liu XX, Shi H, et al. NLRP3 inflammasome, an immune-inflammatory target in pathogenesis and treatment of cardiovascular diseases [J]. *Clin Transl Med*. 2020;10(1):91~106. doi:10.1002/ctm2.13
13. Chen ZX. *Correlation of NLRP3, Caspase-1, and IL-1β Expression in Chronic Heart Failure[D]*. Hangzhou Normal University; 2022.
14. Gao RF, Shi HR, Chang SC, et al. The selective NLRP3-inflammasome inhibitor MCC950 reduces myocardial fibrosis and improves cardiac remodeling in a mouse model of myocardial infarction[J]. *Int Immunopharmacol*. 2019;74:105575. doi:10.1016/j.intimp.2019.04.022
15. Shen S, Duan JF, Hu JX, et al. Colchicine alleviates inflammation and improves diastolic dysfunction in heart failure rats with preserved ejection fraction[J]. *Eur J Pharmacol*. 2022;929:175126. doi:10.1016/j.ejphar.2022.175126
16. Li LL, Gao P, Tang XR, et al. CB1R-stabilized NLRP3 inflammasome drives antipsychotics cardiotoxicity[J]. *Signal Transduct Target Ther*. 2022;7 (1):190. doi:10.1038/s41392-022-01018-7
17. Guler AT, Waaijer CJ, Palmblad M. Scientific workflows for bibliometrics[J]. *Scientometrics*. 2016;107:385~398. doi:10.1007/s11192-016-1885-6
18. Song LX, Zhang J, Ma D, et al. A Bibliometric and Knowledge-Map Analysis of Macrophage Polarization in Atherosclerosis From 2001 to 2021 [J]. *Front Immunol*. 2022;13:910444. doi:10.3389/fimmu.2022.910444
19. Chen Y, Chen CM, Liu ZY, et al. Methodological Functions of the CiteSpace Knowledge Graph[J]. *Sci Res*. 2015;33(02):242~253.
20. Wang ML, Zhao MM, Yu JP, et al. MCC950, a Selective NLRP3 Inhibitor, Attenuates Adverse Cardiac Remodeling Following Heart Failure Through Improving the Cardiometabolic Dysfunction in Obese Mice[J]. *Front Cardiovasc Med*. 2022;9:727474. doi:10.3389/fcvm.2022.727474
21. Mastrocola R, Penna C, Tullio F, et al. Pharmacological Inhibition of NLRP3 Inflammasome Attenuates Myocardial Ischemia/Reperfusion Injury by Activation of RISK and Mitochondrial Pathways[J]. *Oxid Med Cell Longev*. 2016;2016:5271251. doi:10.1155/2016/5271251
22. Sun X, Duan JX, Gong CY, et al. Colchicine Ameliorates Dilated Cardiomyopathy Via SIRT2-Mediated Suppression of NLRP3 Inflammasome Activation[J]. *J Am Heart Assoc*. 2022;11(13):e25266. doi:10.1161/JAHA.122.025266
23. Abbate A, Toldo S, Marchetti C, et al. Interleukin-1 and the Inflammasome as Therapeutic Targets in Cardiovascular Disease[J]. *Circ Res*. 2020;126 (9):1260~1280. doi:10.1161/CIRCRESAHA.120.315937
24. Jiang JJ, Gu XP, Wang HF, et al. Resveratrol improves cardiac function and left ventricular fibrosis after myocardial infarction in rats by inhibiting NLRP3 inflammasome activity and the TGF- β 1/SMAD2 signaling pathway. *PeerJ*. 2021;9:e11501. doi:10.7717/peerj.11501
25. Du YQ, Gu X, Meng HY, et al. Muscone improves cardiac function in mice after myocardial infarction by alleviating cardiac macrophage-mediated chronic inflammation through inhibition of NF-kappaB and NLRP3 inflammasome[J]. *Am J Transl Res*. 2018;10(12):4235~4246.
26. Zhou T, Xiang DK, Li SN, et al. MicroRNA-495 Ameliorates Cardiac Microvascular Endothelial Cell Injury and Inflammatory Reaction by Suppressing the NLRP3 Inflammasome Signaling Pathway[J]. *Cell Physiol Biochem*. 2018;49(2):798~815. doi:10.1159/000493042
27. Bracey NA, Beck PL, Muruve DA, et al. The Nlrp3 inflammasome promotes myocardial dysfunction in structural cardiomyopathy through interleukin-1beta[J]. *Exp Physiol*. 2013;98(2):462~472. doi:10.1113/expphysiol.2012.068338
28. Yue RC, Zheng ZY, Luo Y, et al. NLRP3-mediated pyroptosis aggravates pressure overload-induced cardiac hypertrophy, fibrosis, and dysfunction in mice: cardioprotective role of irisin[J]. *Cell Death Discov*. 2021;7(1):50. doi:10.1038/s41420-021-00434-y
29. Wang FH, Liang QQ, Ma YX, et al. Silica nanoparticles induce pyroptosis and cardiac hypertrophy via ROS/NLRP3/Caspase-1 pathway[J]. *Free Radic Biol Med*. 2022;182:171~181. doi:10.1016/j.freeradbiomed.2022.02.027
30. Kobayashi M, Usui-Kawanishi F, Karasawa T, et al. The cardiac glycoside ouabain activates NLRP3 inflammasomes and promotes cardiac inflammation and dysfunction[J]. *PLoS One*. 2017;12(5):e176676. doi:10.1371/journal.pone.0176676
31. Wang YX, Hu WH, Yuan YQ. Protein Arginine Methyltransferase 5 (PRMT5) as an Anticancer Target and Its Inhibitor Discovery[J]. *J Med Chem*. 2018;61(21):9429~9441. doi:10.1021/acs.jmedchem.8b00598
32. Chen M, Yi B, Sun JX. Inhibition of cardiomyocyte hypertrophy by protein arginine methyltransferase 5[J]. *J Biol Chem*. 2014;289 (35):24325~24335. doi:10.1074/jbc.M114.577494
33. Penela P, Inserte J, Ramos P, et al. Degradation of GRK2 and AKT is an early and detrimental event in myocardial ischemia/reperfusion[J]. *EBioMedicine*. 2019;48:605~618. doi:10.1016/j.ebiom.2019.09.019
34. Penela P, Ribas C, Sanchez-Madrid F, et al. G protein-coupled receptor kinase 2 (GRK2) as a multifunctional signaling hub[J]. *Cell mol Life Sci*. 2019;76(22):4423~4446. doi:10.1007/s00018-019-03274-3
35. Murga C, Arcones AC, Cruces-Sande M, et al. G Protein-Coupled Receptor Kinase 2 (GRK2) as a Potential Therapeutic Target in Cardiovascular and Metabolic Diseases[J]. *Front Pharmacol*. 2019;10:112. doi:10.3389/fphar.2019.00112
36. Ciccarelli M, Sorriento D, Fiordelisi A, et al. Pharmacological inhibition of GRK2 improves cardiac metabolism and function in experimental heart failure[J]. *ESC Heart Fail*. 2020;7(4):1571~1584. doi:10.1002/ehf2.12706
37. Rengo G, Perrone-Filardi P, Femminella GD, et al. Targeting the beta-adrenergic receptor system through G-protein-coupled receptor kinase 2: a new paradigm for therapy and prognostic evaluation in heart failure: from bench to bedside[J]. *Circ Heart Fail*. 2012;5(3):385~391. doi:10.1161/CIRCHEARTFAILURE.112.966895
38. Sun XJ, Zhou ML, Wen GY, et al. Paroxetine Attenuates Cardiac Hypertrophy Via Blocking GRK2 and ADRB1 Interaction in Hypertension[J]. *J Am Heart Assoc*. 2021;10(1):e16364. doi:10.1161/JAHA.120.016364
39. Liu J, Li XL, Ding L, et al. GRK2 participation in cardiac hypertrophy induced by isoproterenol through the regulation of Nrf2 signaling and the promotion of NLRP3 inflammasome and oxidative stress[J]. *Int Immunopharmacol*. 2023;117:109957. doi:10.1016/j.intimp.2023.109957
40. Dong YH, Xu S, Liu J, et al. Non-coding RNA-linked epigenetic regulation in cardiac hypertrophy[J]. *Int J Biol Sci*. 2018;14(9):1133~1141. doi:10.7150/ijbs.26215
41. Zhou LY, Liu JP, Wang K, et al. Mitochondrial function in cardiac hypertrophy[J]. *Int J Cardiol*. 2013;167(4):1118~1125. doi:10.1016/j.ijcard.2012.09.082
42. Neubauer S. The failing heart–an engine out of fuel[J]. *N Engl J Med*. 2007;356(11):1140~1151. doi:10.1056/NEJMra063052
43. Aubert G, Vega RB, Kelly DP. Perturbations in the gene regulatory pathways controlling mitochondrial energy production in the failing heart[J]. *Biochim Biophys Acta*. 2013;1833(4):840~847. doi:10.1016/j.bbamcr.2012.08.015
44. Zhou RB, Yazdi AS, Menu P, et al. A role for mitochondria in NLRP3 inflammasome activation[J]. *Nature*. 2011;469(7329):221~225. doi:10.1038/nature09663
45. Li L, Cui YJ, Liu Y, et al. ATP6AP2 knockdown in cardiomyocyte deteriorates heart function via compromising autophagic flux and NLRP3 inflammasome activation[J]. *Cell Death Discov*. 2022;8(1):161. doi:10.1038/s41420-022-00967-w

46. Chen Y, Zeng MY, Zhang Y, et al. Nlrp3 Deficiency Alleviates Angiotensin II-Induced Cardiomyopathy by Inhibiting Mitochondrial Dysfunction [J]. *Oxid Med Cell Longev*. 2021;2021:6679100. doi:10.1155/2021/6679100
47. Toldo S, Abbate A. The NLRP3 inflammasome in acute myocardial infarction[J]. *Nat Rev Cardiol*. 2018;15(4):203~214. doi:10.1038/nrcardio.2017.161
48. Zeng C, Duan FQ, Hu J, et al. NLRP3 inflammasome-mediated pyroptosis contributes to the pathogenesis of non-ischemic dilated cardiomyopathy [J]. *Redox Biol*. 2020;34:101523. doi:10.1016/j.redox.2020.101523
49. Zhang JM, Yu RQ, Wu FZ, et al. BMP-2 alleviates heart failure with type 2 diabetes mellitus and doxorubicin-induced AC16 cell injury by inhibiting NLRP3 inflammasome-mediated pyroptosis[J]. *Exp Ther Med*. 2021;22(2):897. doi:10.3892/etm.2021.10329
50. Imazio M, Nidorf M. Colchicine and the heart[J]. *Eur Heart J*. 2021;42(28):2745~2760. doi:10.1093/eurheartj/ehab221
51. Deftereos S, Giannopoulos G, Panagopoulou V, et al. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study[J]. *JACC Heart Fail*. 2014;2(2):131~137. doi:10.1016/j.jchf.2013.11.006
52. Van Tassell B, Canada J, Arena R, et al. Colchicine in stable chronic heart failure[J]. *JACC Heart Fail*. 2014;2(5):538. doi:10.1016/j.jchf.2014.04.009
53. Wohlford GF, Van Tassell BW, Billingsley HE, et al. Phase 1B, Randomized, Double-Blinded, Dose Escalation, Single-Center, Repeat Dose Safety and Pharmacodynamics Study of the Oral NLRP3 Inhibitor Dapansutrile in Subjects With NYHA II-III Systolic Heart Failure[J]. *J Cardiovasc Pharmacol*. 2020;77(1):49~60. doi:10.1097/FJC.0000000000000931
54. Van Tassell BW, Arena R, Biondi-Zoccai G, et al. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study)[J]. *Am J Cardiol*. 2014;113(2):321~327. doi:10.1016/j.amjcard.2013.08.047
55. Abbate A, Van Tassell BW, Biondi-Zoccai G, et al. Effects of interleukin-1 blockade with anakinra on adverse cardiac remodeling and heart failure after acute myocardial infarction [from the Virginia Commonwealth University-Anakinra Remodeling Trial (2) (VCU-ART2) pilot study][J]. *Am J Cardiol*. 2013;111(10):1394~1400. doi:10.1016/j.amjcard.2013.01.287
56. Van Tassell B, Mihalick V, Thomas G, et al. Rationale and design of interleukin-1 blockade in recently decompensated heart failure (REDHART2): a randomized, double blind, placebo controlled, single center, Phase 2 study[J]. *J Transl Med*. 2022;20(1):270. doi:10.1186/s12967-022-03466-9
57. Rosca MG, Vazquez EJ, Kerner J, et al. Cardiac mitochondria in heart failure: decrease in respirasomes and oxidative phosphorylation[J]. *Cardiovasc Res*. 2008;80(1):30~39. doi:10.1093/cvr/cvn184
58. Zhong ZY, Liang S, Sanchez-Lopez E, et al. New mitochondrial DNA synthesis enables NLRP3 inflammasome activation[J]. *Nature*. 2018;560(7717):198~203. doi:10.1038/s41586-018-0372-z
59. Dan DJ, Alvarez LA, Zhang X, et al. Reactive oxygen species and mitochondria: a nexus of cellular homeostasis[J]. *Redox Biol*. 2015;6:472~485. doi:10.1016/j.redox.2015.09.005
60. Wang D, F HL, Yu X, et al. The role of NLRP3 inflammatory vesicles in heart failure and the research progress of Chinese medicine intervention [J]. *Chin J Trad Chin Med*. 2024;49(04):894–901.