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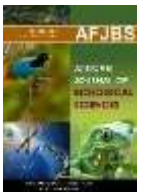

Error-Prone DNA Synthesis and Accumulation of Single Nucleotide Gaps by DNA Polymerase β Leads to Cancer: A Bibliometric Analysis

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Abstract

DNA Pol β is essential for DNA repair and maintenance of genomic integrity, its dysregulation or malfunction can contribute to cancer development by increasing mutation rates, promoting genomic instability, and altering cellular signaling pathways. Understanding the role of Pol β in cancer biology may offer insights into novel therapeutic strategies for cancer treatment. The bibliometric analysis using Dimension AI followed by VOSviewer delves into the study of error-prone DNA synthesis and the accumulation of single nucleotide gaps caused by DNA polymerase beta, with a focus on its association with cancer. Since 2020, a substantial increase in publications on this topic has been observed, particularly in 2021, totaling 4821 publications. These include various types such as book chapters, edited books, articles, monographs, preprints, and proceedings, with a total of 9631 publications. Biomedical and Clinical Sciences emerged as the dominant research field with 1702 publications. Co-authorship analysis highlighted Jonkers, Jos as the leading author with 5 documents and 152 citations. The United States led in contributions with 357 documents and 5,396 citations, followed by India with 95 documents and 995 citations. The analysis identified 7 clusters of contributing countries. The International Journal of Molecular Sciences emerged as the most cited source with 37 documents and 762 citations. Harvard University led in co-authorship analysis with 30 documents and 654 citations. Co-citation analysis revealed Hanahan, D, et al. (2011), Jackson,Sp, et al. (2009), and Chatterjee, N, et al. (2017) as top references. The Co-occurrence analysis of terms highlighted 'repair' as the most frequent term, appearing 159 times. Overall, the study provides comprehensive insights into the landscape of research on error-prone DNA synthesis and its implications in cancer, identifying key contributors, sources, and trends in the field.

Keywords: Pol β, cancer, therapeutic, bibliometric, Dimension AI, VOSviewer, error-proneDNA synthesis

Introduction

Cancer encompasses a collection of ailments characterized by the uncontrolled proliferation and dissemination of abnormal cells within the body. In a healthy body, cells grow, divide, and expire in an orderly fashion, but cancer disrupts this regulated process. Once cells become cancerous, they persistently divide and grow without restraint, forming clusters of tissue known as tumors (Fares, J. *et al* 2020). Depending on their size and location, these tumors can impede the normal functioning of the body. Cancer can originate from nearly any type of cell in the body and can metastasize to other regions through either the bloodstream or the lymphatic system. This process, referred to as metastasis, allows cancer to spread throughout the body (Massague, J. *et al* 2021). With more than 100 distinct types of cancer, each presents its unique symptoms, risk factors, and treatment options. Various factors contribute to the development of cancer, including genetic predisposition, exposure to carcinogens like tobacco smoke, ultraviolet radiation, and certain chemicals, as well as unhealthy lifestyle choices such as an inadequate diet, lack of physical activity, and excessive alcohol consumption. Additionally, certain infections like human papillomavirus and hepatitis B and C viruses can also increase the risk of developing cancer (Luo, C. *et al* 2022). The treatment of cancer depends on the specific type and stage of the disease. It may involve surgical intervention, chemotherapy, radiation therapy, immunotherapy, targeted therapy, hormone therapy, or a combination of these approaches. Early detection and prompt treatment significantly enhance the prognosis and outcomes for individuals diagnosed with cancer. In eukaryotes, Pol β a key participant in DNA repair pathways, functions in both base excision repair (BER) and non-homologous end joining (NHEJ) (Hindi, N. *et al* 2021). Despite its lack of proofreading capability, it maintains a reasonable level of accuracy during DNA replication. The study of its fidelity mechanisms involves examining the dynamic changes in its conformation when interacting with DNA and deoxynucleoside triphosphates. Recent studies have linked germline and somatic Pol β variants to diseases such as cancer and autoimmunity (Solís Moruno, M. 2021). These variants promote genomic instability through mechanisms like error-prone DNA synthesis and the accumulation of single nucleotide gaps, leading to replication stress. Previous studies highlight the structure and function of Pol β, elucidating how changes in its structure caused by variants contribute to genomic instability, mutagenesis, and disease (Sawyer, D. L., & Sweasy, J. B. 2022). The implications of these findings extend to cancer progression and treatment outcomes, positioning Pol β as a critical target for further research in understanding and addressing these conditions. In recent years, there has been significant interest in the scientific community

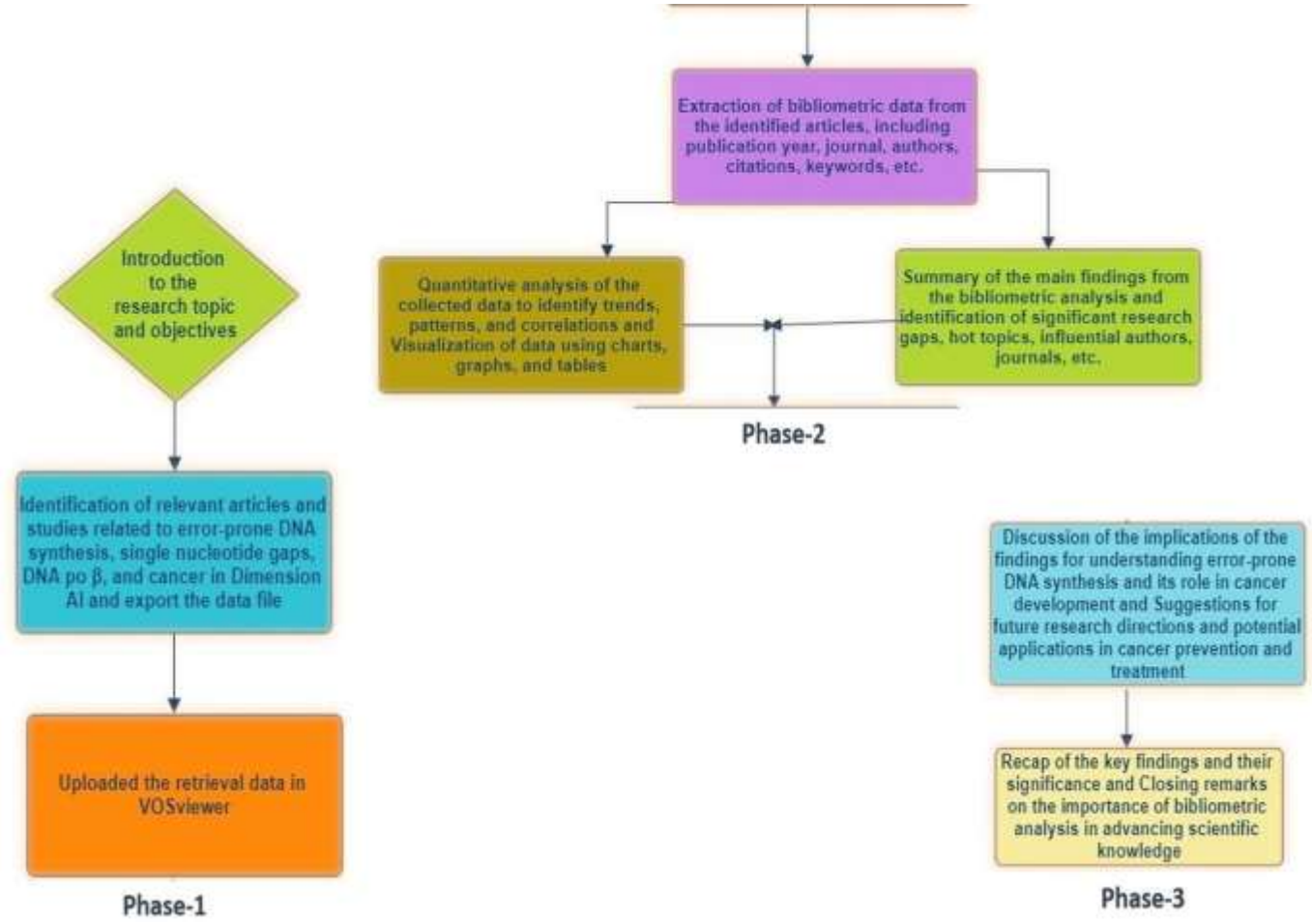
regarding the relationship between DNA replication accuracy and cancer development. Central to this investigation is the enzyme DNA polymerase β, which plays a vital role in DNA repair and synthesis. Understanding the consequences of error-prone DNA synthesis and the accumulation of single nucleotide gaps facilitated by Pol β is crucial for understanding cancer progression (Czajkowski, D. *et al* 2022).

To explore the extensive literature on this topic, a bibliometric analysis was conducted in collaboration with Dimension AI and VOSviewer software (Oyewola, D. *et al* 2022). By utilizing advanced data mining techniques, the study aims to gain insights into current research trends and identify potential areas for future exploration. Through a systematic examination of academic publications, citation networks, and thematic clusters, this analysis aims to illuminate how errors in DNA synthesis, mediated by Pol β, contribute to cancer initiation, progression, and metastasis. By quantitatively assessing the impact of relevant scientific literature, the study aims to provide valuable insights for researchers, clinicians, and policymakers in this important field (Lv, H., Gao, Z. *et al* 2022).

Methodology

Conducting a captivating study on the impact of errors induced by DNA polymerase β on cancer development requires a meticulous analysis. The study employed tools such as Dimension AI and VOSviewer to facilitate the navigation of the research process (Williams, B. 2020). The relevant data was collected from academic databases from Dimension AI by including appropriate keywords such as "DNA polymerase β," "cancer," "DNA synthesis," and others related to the topic. The primary focus of the study was on error-prone DNA synthesis and the build-up of single nucleotide gaps by DNA polymerase β, resulting in cancer development in Dimension AI. Upon accessing the complimentary version of the software, the email filter has been in place since 2020. Next, Dimension AI was employed to extract bibliometric data, which can provide valuable insights into citation counts, authors, journals, and more. Utilizing the chosen keywords to search for articles and analyze citation metrics, collaboration networks, and trending topics associated with this particular research. After the data retrieval from Dimension AI, was transferred it to VOSviewer for visualization purposes. With VOSviewer, created visual representations such as co-authorship networks, co-citation networks, keyword co-occurrence maps, etc. (Qiang, Y. *et al* 2022). These visualizations were analyzed to identify clusters of highly cited articles, influential authors, and emerging research trends etc. After generating the visualizations, interpretation of the results and gain insights

into the research landscape concerning DNA polymerase β and cancer were analysed and the key contributors, influential papers, and gaps in the existing literature etc. also established. By following these step-by-step guidelines, conducted a comprehensive bibliometric analysis to comprehend the relationship between errors induced by DNA polymerase β and cancer development (Yin, Hua, *et al* 2022) The relevant study and data retrieval link can be found at https://export.digital-science.com/2024-04 22/08a971cb04f4d3b2da91f5472b6c176c/Dimensions-Publication-2024-04-22_09-29-59.csv.zip. The working procedure has been summarized in three phases as follows:



Result analysis and Discussion

Since 2020, this study has been centered on the examination of error-prone DNA synthesis and the accumulation of single nucleotide gaps caused by DNA polymerase beta, which is closely linked to cancer (Canitrot, Yvan, *et al* 2000). The year 2021 has marked a significant increase in publications on this subject, with a total of 4821 presented in Fig. 1a. In terms of publication types, analysis has identified 5612 book chapters, 2646 edited books, 1048 articles, 248

monographs, 75 preprints, and 2 proceedings, resulting in a total of 9631 publications represented in Fig. 1b.

Once again, Biomedical and Clinical Sciences reign supreme in the realm of research, boasting an impressive publication count of 1702 Johan, (Muhammad Farid, *et al*). In the co-authorship analysis, the first author with 5 documents and 152 citations is Jonkers, Jos presented in Fig. 2 (Dias, Mariana Paes, *et al* 2021). The threshold values set were a minimum of 5 documents and a minimum of zero citations mentioned in Table 1.

During the co-authorship analysis as a unit of analysis of contributing countries, 66 countries were identified as the unit of analysis, with 44 of them meeting the minimum threshold requirement of 5 documents per country. The United States ranked first with 357 documents and 5,396 citations, while India came in second with 95 documents and 995 citations (Özen Çınar, İ. 2020). A total of 7 clusters with 43 items were observed, with the major contributing countries highlighted in Figure 3 and Table 2.

In the analysis of citations as a unit of sources, the International Journal of Molecular Sciences stands out as the leader (Grimm, D. 2022; Buttiron Webber, Tania, *et al* 2023), with 37 documents and 762 citations, as shown in Fig.4 and Table 2. A total of 3 clusters containing 18 items were identified, with a threshold value of 5 for both documents and citations within a journal. Out of the 515 sources, 39 met this threshold.

Once again, Harvard University emerged as the leading organization in co-authorship analysis, with 30 documents and 654 citations. Similar to source analysis, the threshold value was established. Out of the 1376 organizations, 63 met the threshold, and the main contributors are presented in Table 3 and Fig. 5. A total of 9 clusters were identified (Kerr, David, *et al* 2022; Hosny, Ahmed, *et al* 2022).

The co-citation analysis focused on the cited references (Hanahan, D, *et al* 2011), (Jackson, Sp, *et al* 2009), and (Chatterjee, N, *et al* 2017), which emerged as the top three references with 57, 53, and 48 citations respectively. These findings are presented in Table 3 and Fig. 6. A total of 4 clusters, comprising 41 items, were identified. The threshold parameter used was a minimum of 20 citations for a cited reference, and 41 references met this threshold. Four clusters containing a total of 41 items were identified for co-occurrence analysis. A minimum term occurrence of 10 was chosen, with 291 terms meeting this threshold. The term 'repair' was the most frequently used, appearing 159 times, and the result of co-occurrence has been presented in Fig. 7. (Sobol, Robert W., *et al* 2000; Ceccaldi, Raphael, *et al* 2015).

The future scope

The future scope of this research could encompass several directions:

Clinical Implications: Further investigation into the specific mutations or genomic alterations caused by error-prone DNA synthesis and single nucleotide gaps could provide insights into personalized cancer treatments. Targeted therapies tailored to individual genetic profiles could be developed to mitigate the effects of these errors and prevent cancer progression.

Drug Development: Identifying small molecules or inhibitors that can modulate the activity of DNA polymerase β or enhance its fidelity could be a promising avenue for drug development. These compounds could potentially serve as adjuvant therapies to conventional cancer treatments or even as standalone treatments for certain types of cancer.

Diagnostic Biomarkers: Exploring the association between error-prone DNA synthesis, single nucleotide gaps, and specific types of cancer could lead to the discovery of diagnostic biomarkers. These biomarkers could be utilized for early cancer detection, monitoring disease progression, and predicting treatment response.

Mechanistic Studies: Further elucidating the molecular mechanisms underlying error-prone DNA synthesis and the role of DNA polymerase β in cancer development could uncover novel biological pathways and therapeutic targets. This could involve employing advanced molecular biology techniques, such as CRISPR-Cas9 genome editing or single-cell sequencing, to dissect these complex processes at the cellular and molecular level.

Translational Research: Bridging the gap between basic research findings and clinical applications is essential. Collaborations between basic scientists, clinicians, and pharmaceutical companies could facilitate the translation of research discoveries into tangible benefits for patients, such as improved treatment outcomes and quality of life.

Data Integration and Systems Biology: Integrating data from various omics platforms, including genomics, transcriptomics, and proteomics, could provide a comprehensive understanding of the interconnected molecular networks involved in cancer development. Systems biology approaches could help unravel the complexity of cancer biology and identify key nodes or pathways that can be targeted for therapeutic intervention.

Research Limitations

This methods may also have some limitations:

Data Limitations: Bibliometric analyses rely heavily on the quality and availability of data. If the dataset used for analysis is limited in scope or biased towards certain types of publications or journals, it could affect the robustness and generalizability of the findings.

Publication Bias: There may be a bias towards published literature, which could skew the analysis towards studies that have been successfully published. This could lead to an incomplete representation of the research landscape, particularly if studies with negative or null results are underrepresented.

Interpretation Bias: The interpretation of bibliometric data relies on the expertise and subjectivity of the researchers conducting the analysis. Different researchers may interpret the same data differently, leading to potential biases in the conclusions drawn from the analysis.

Scope of Analysis: The scope of the bibliometric analysis may be limited to certain databases, time periods, or geographic regions, which could influence the comprehensiveness of the findings. Additionally, the choice of keywords and search terms used to retrieve relevant publications may impact the inclusivity of the analysis.

Causality vs. Correlation: While bibliometric analyses can identify trends and associations between variables, they cannot establish causality. In the case of this research, while it may identify a correlation between error-prone DNA synthesis by DNA polymerase β and cancer development, further experimental studies are needed to establish a causal relationship and elucidate the underlying mechanisms.

Dynamic Nature of Research: Research trends and publication patterns are dynamic and subject to change over time. A bibliometric analysis provides a snapshot of the research landscape at a particular point in time, but it may not capture ongoing developments or emerging trends in the field.

Lack of Contextual Information: Bibliometric analyses typically focus on quantitative data such as publication counts, citation metrics, and co-authorship networks. While these metrics provide valuable insights into the structure and impact of the research landscape, they may lack the contextual information necessary to fully understand the underlying factors driving the observed trends.

Conclusion

The bibliometric analysis on error-prone DNA synthesis and the accumulation of single nucleotide gaps by DNA polymerase β reveals a significant focus on understanding its implications in cancer research. The study, spanning from 2020 to 2021, highlights a notable increase in publications, totaling 9631 across various formats. Biomedical and Clinical Sciences emerge as the primary field of investigation, with 1702 publications. Co-authorship analysis identifies Jonkers, Jos as a leading author, while the United States leads in contributions, followed by India. The International Journal of Molecular Sciences stands out as a key source, and Harvard University emerges as a prominent contributor. Top cited references and prevalent terms emphasize the global research efforts to comprehend the complexities of error-prone DNA synthesis and its role in cancer development. This study emphasizes the importance of continuous research and collaboration in understanding and mitigating the impact of DNA polymerase beta on cancer. By employing bibliometric analysis, researchers and policymakers can gain valuable insights to inform decision-making and progress towards a more therapeutic future.

Ethical approval Not applicable.

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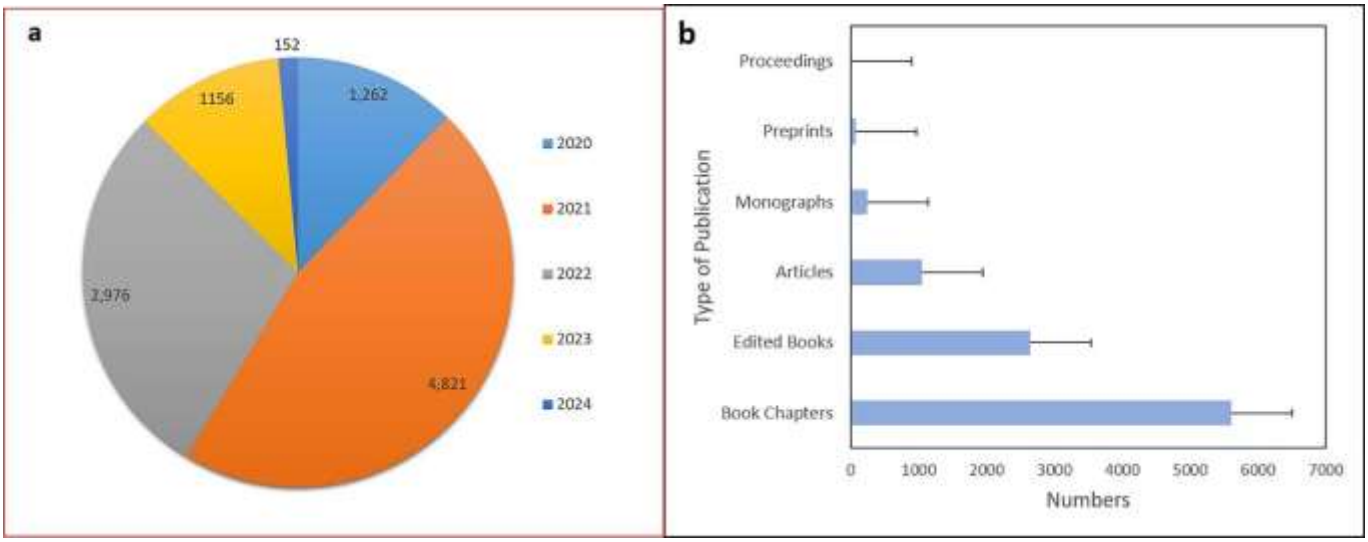
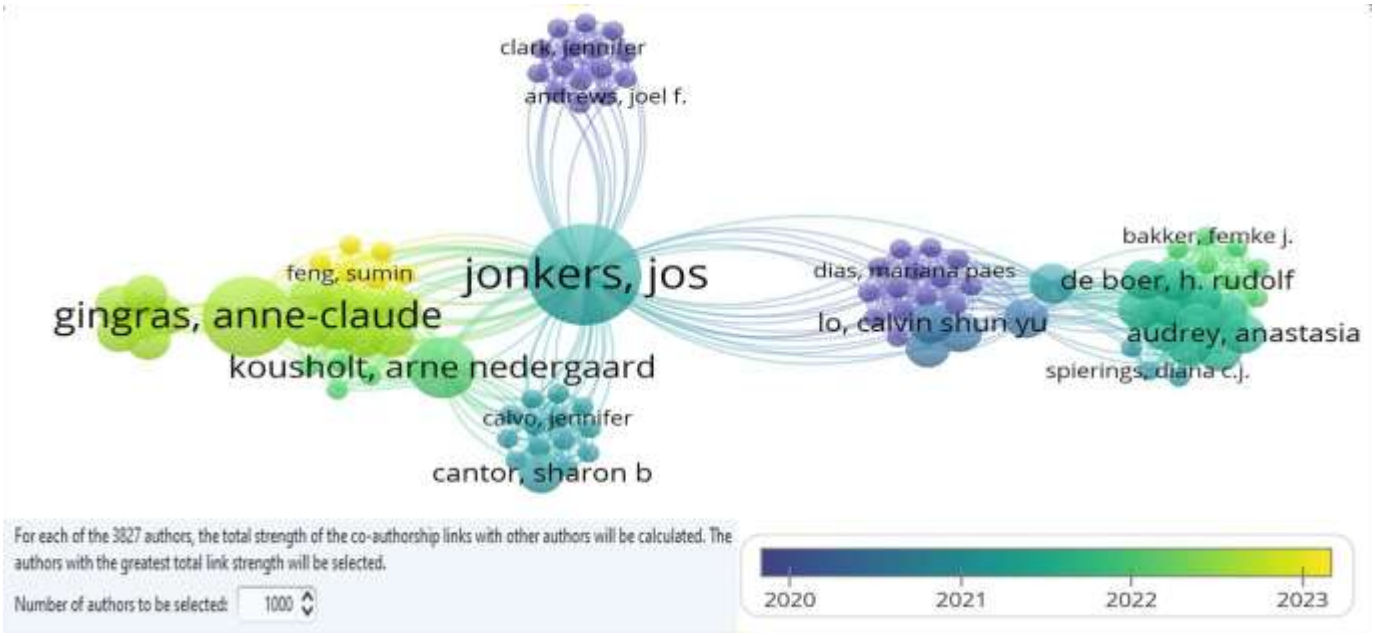
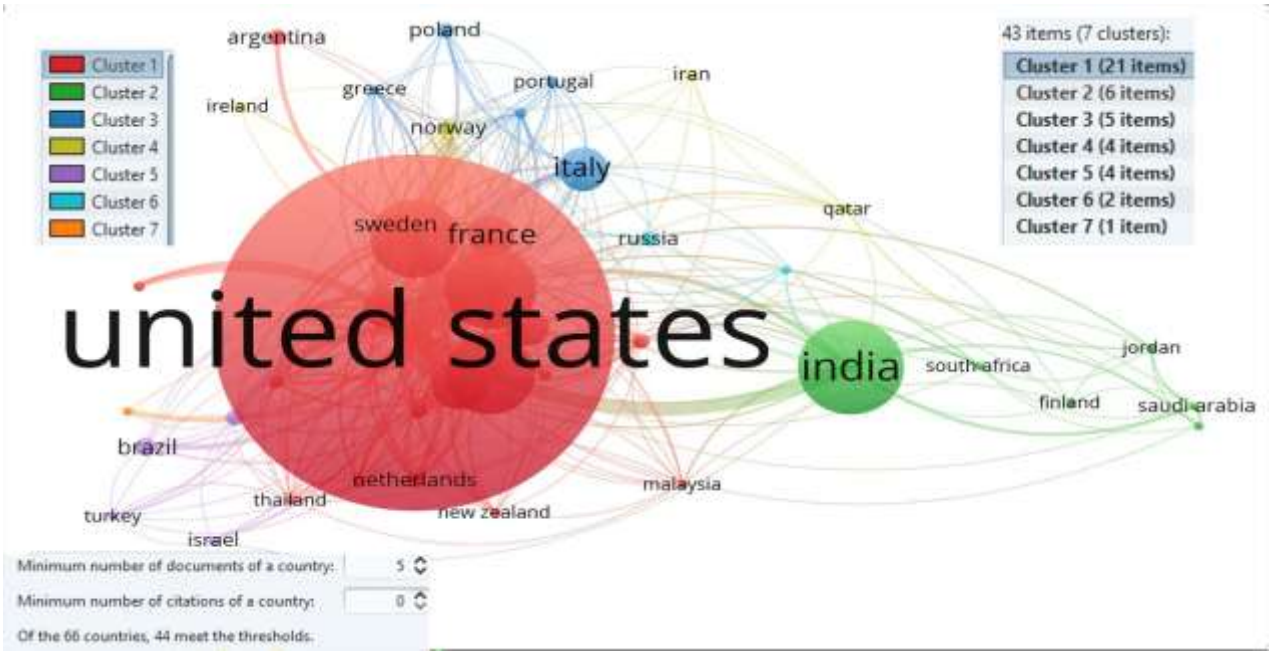
Figures and Captions:



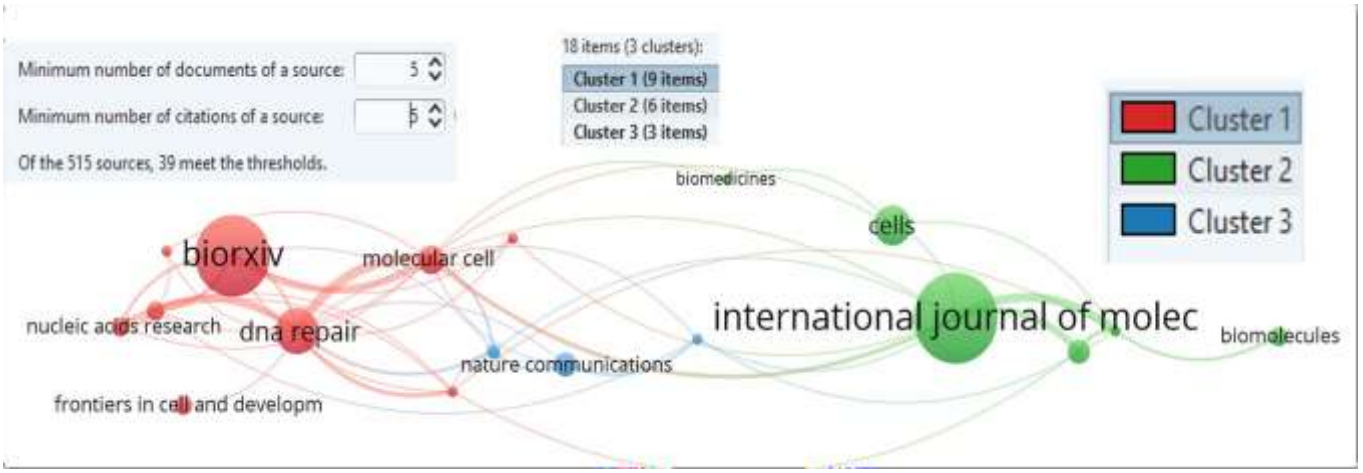
"Figure 1a": Numbers of publications in different years, "Figure 1b": Numbers of different types of publication



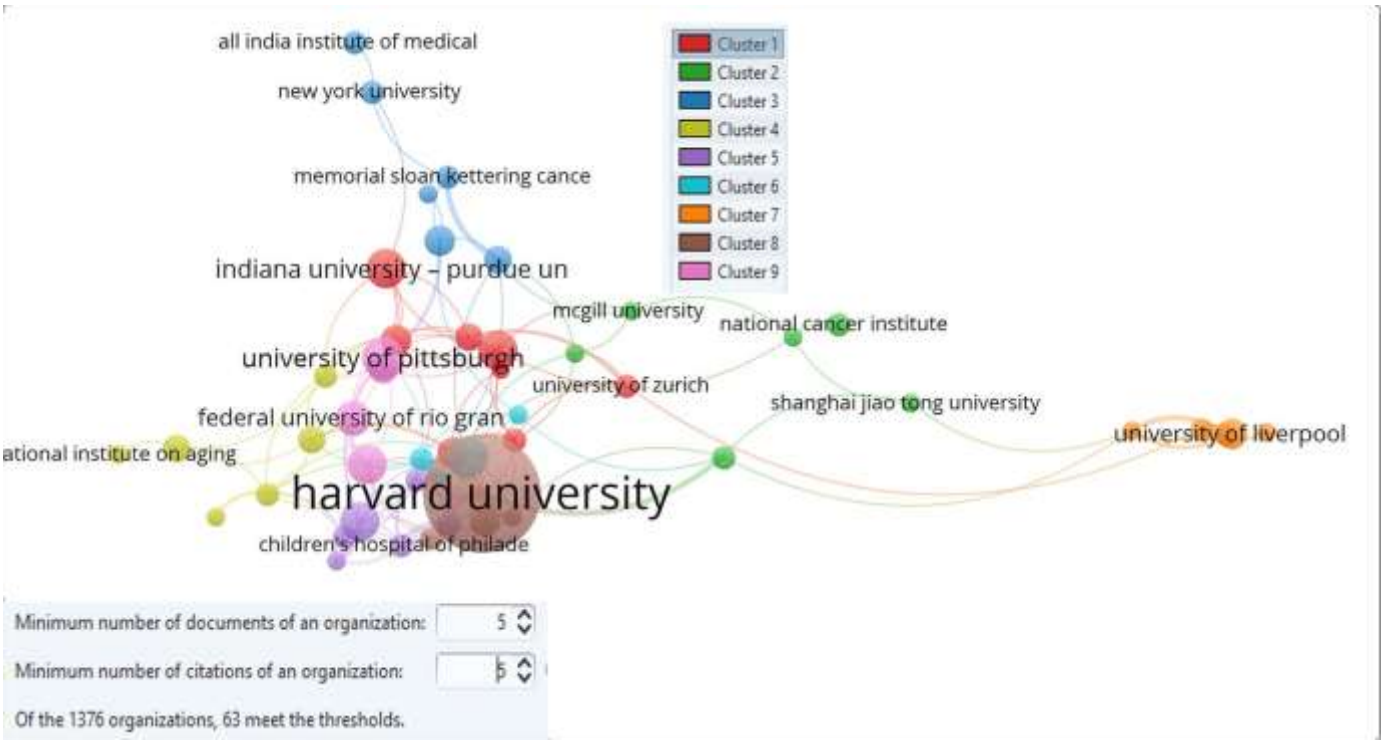
"Figure 2": Co-authorship analysis as a unit of Author analysis



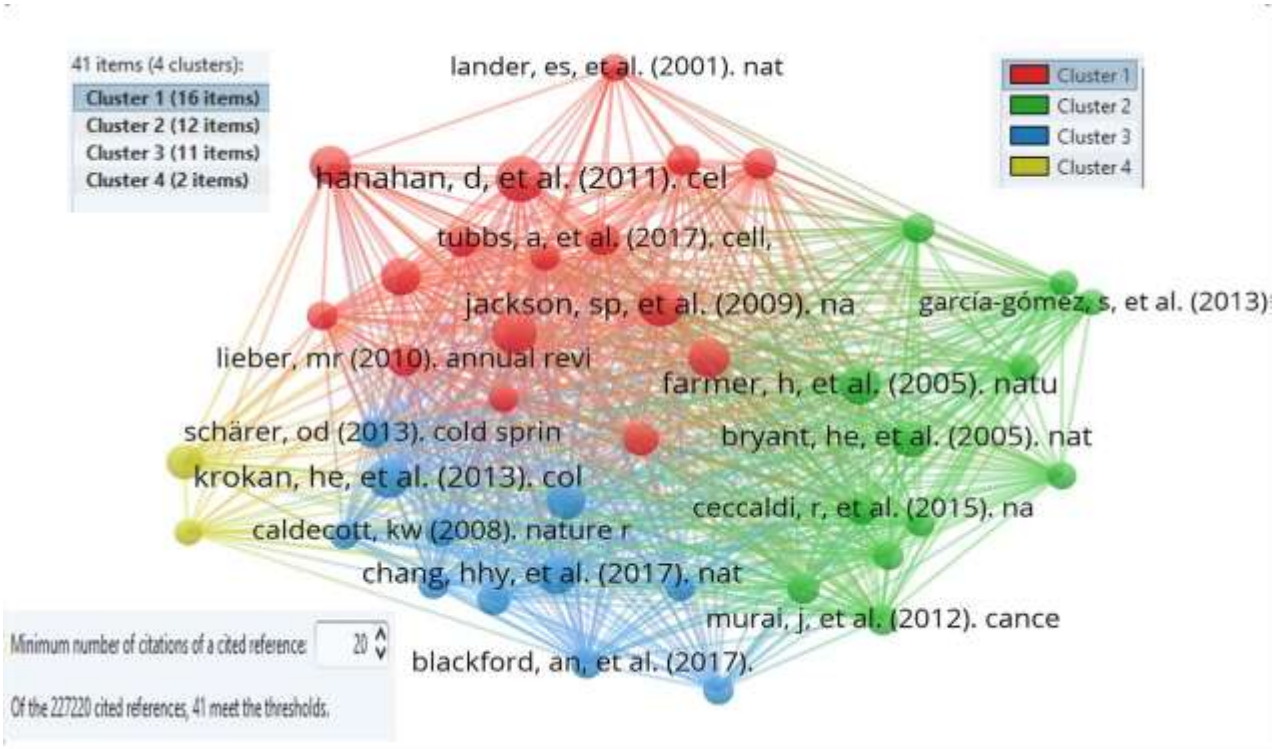
"Figure 3": Co-authorship analysis as a unit of Country



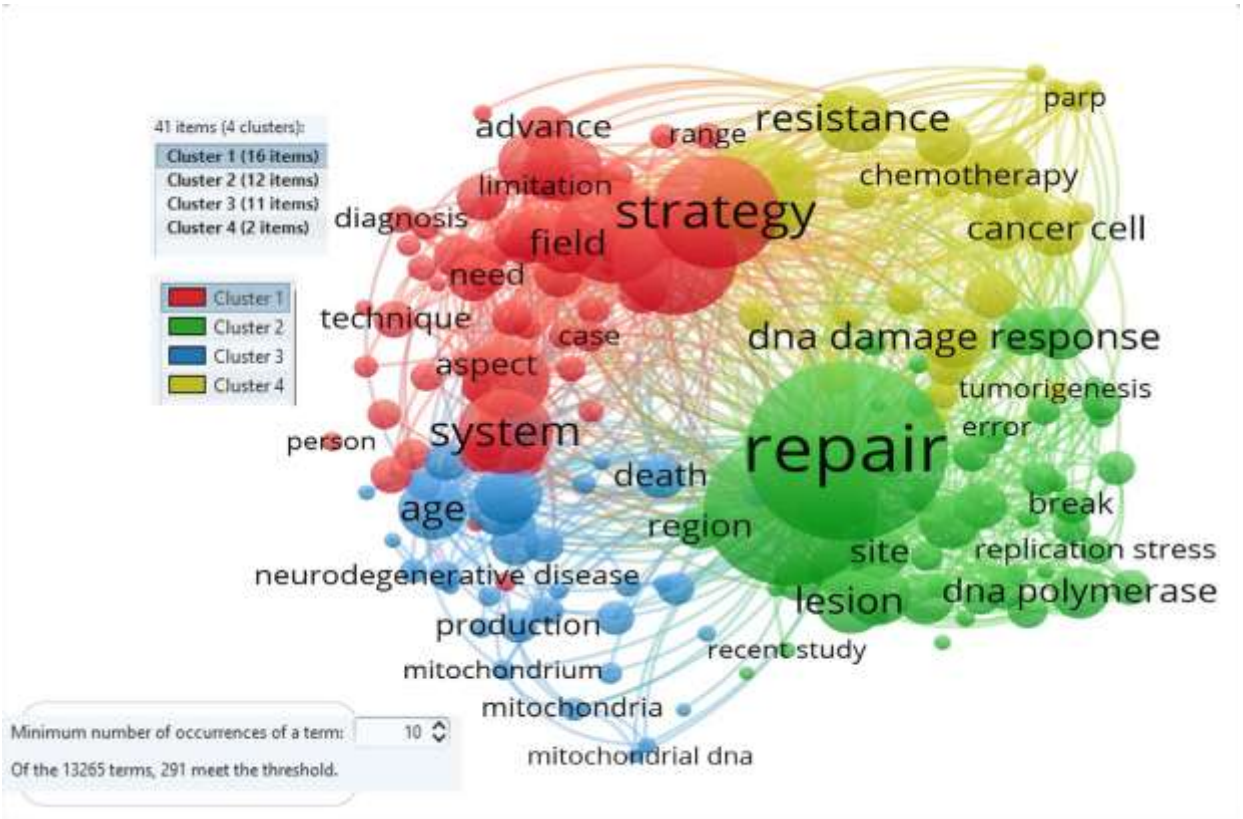
"Figure 4": Citation analysis as a unit of Sources



"Figure 5": Co-authorship analysis as a unit of Organizations



"Figure 6": Co-citations analysis as a unit of cited references



"Figure 7": Analysis of Co-occurrence

Tables:

Table 1. Top 15 Research fields, and Co-authorship analysis

Field of Research		**Type of analysis: Co-authorship Unit of analysis: Authors**		
Research category	**Publications**	**Author**	**Citation**	**Documents**
Biomedical and Clinical Sciences	1,702	Jonkers, Jos	152	5
Biological Sciences	1,436	Cağlayan, Melike	62	7
Clinical Sciences	510	Ain, Quratul	58	4
Biochemistry and Cell Biology	501	Tang, Qun	28	5
Genetics	318	Mosammaparast, Nima	14	4
Chemical Sciences	303	Gingras, Anne-claude	8	4
Oncology and Carcinogenesis	267	Koehn, Liam M.	6	6
Health Sciences	243	Woods, Adam J.	2	10
Bioinformatics and Computational Biology	202	Ibarra, Manuel	0	9
Microbiology	192	Bellera, Carolina L.	1	6
Medical Biotechnology	191	Talevi, Alan	1	6
Medicinal and Biomolecular Chemistry	160	Frank, Luiza Abrahão	1	5
Immunology	116	Guterres, Silvia S.	1	4
Pharmacology and Pharmaceutical Sciences	88	Lesko, Lawrence J.	0	6
Reproductive Medicine	76	Pohlmann, Adriana R.	1	4

Table 2. Top 20 Countries and Journals since 2020

Type of analysis: Co-authorship, Unit of analysis: Country			**Type of analysis: Citations, Unit of analysis: Source**		
Country	**Documents**	**Citations**	**Source**	**Documents**	**Citations**
United States	357	5396	International Journal of Molecular Sciences	37	762
India	95	999	Biorxiv	45	33
United Kingdom	82	2218	Cells	16	421
China	81	2061	DNA Repair	19	379
Germany	79	2393	Molecular Cell	12	470
Canada	49	1003	Nature Communications	10	255
Italy	44	897	Cancers	10	514
France	42	1777	Frontiers in Cell and Developmental Biology	8	62
Spain	40	1721	Biomolecules	8	87
Australia	39	647	Nucleic Acids Research	8	43
Brazil	19	318	Genes	8	236
Sweden	19	199	Journal of Biological Chemistry	8	267
Switzerland	17	463	Pediatric Blood & Cancer	7	189
Japan	16	215	Subcellular Biochemistry	7	14
Argentina	16	142	Biomedicines	5	49
Netherlands	15	420	Viruses	5	66
South Korea	15	329	Cell Reports	5	100
Poland	15	239	Frontiers in Immunology	5	63
Austria	14	574	critical reviews in biochemistry and molecular biology	5	51
Norway	14	255	Signal Transduction and Targeted Therapy	5	906

Table 3. Top 20 Organizations and Co-Citation Analysis

Type of analysis: Co-authorship, Unit of analysis: Organization			**Type of analysis: Co-Citation, Unit of analysis: Cited References**	
Name of Organization	**Documents**	**Citations**	**Cited reference**	**Citations**
Harvard University	30	654	hanahan, d, et al. (2011). cell, 144(5), 646-674	57
Indiana University – Purdue University Indianapolis	10	243	jackson, sp, et al. (2009). nature, 461(7267), 1071-1078	53
University of Pittsburgh	11	190	chatterjee, n, et al. (2017). environmental and molecular mutagenesis, 58(5), 235-263	48
Federal University of Rio Grande Do Sul	9	52	farmer, h, et al. (2005). nature, 434(7035), 917-921	44
University of Liverpool	8	249	krokan, he, et al. (2013). cold spring harbor perspectives in biology, 5(4), a012583	43
Mayo Clinic	8	140	lópez-otín, c, et al. (2013). cell, 153(6), 1194-1217	42
University of Zurich	6	259	ciccia, a, et al. (2010). molecular cell, 40(2), 179-204	42
New York University	6	224	lindahl, t (1993). nature, 362(6422), 709-715	40
Indian Institute of Science Bangalore	6	109	chang, hhy, et al. (2017). nature reviews molecular cell biology, 18(8), 495-506	40
National Cancer Institute	6	103	bryant, he, et al. (2005). nature, 434(7035), 913-917	38
Children's Hospital of Philadelphia	6	47	marteijn, ja, et al. (2014). nature reviews molecular cell biology, 15(7), 465-481	36
all India Institute of Medical Sciences	6	9	jinek, m, et al. (2012). science, 337(6096), 816-821	33
Johns Hopkins University	5	468	scully, r, et al. (2019). nature reviews molecular cell biology, 20(11), 698-714	31
Shanghai Jiao Tong University	5	205	tubbs, a, et al. (2017). cell, 168(4), 644-656	30
Oslo University Hospital	5	130	lieber, mr (2010). annual review of biochemistry, 79(1), 181-211	29
National Institute on Aging	5	111	schärer, od (2013). cold spring harbor perspectives in biology, 5(10), a012609	28
Sichuan university	5	78	alexandrov, lb, et al. (2013). nature, 500(7463), 415-421	28
University of Chinese Academy of Sciences	5	63	alexandrov, lb, et al. (2020). nature, 578(7793), 94-101	28
University Medical Center of the Johannes Gutenberg University Mainz	5	41	hoeijmakers, jhj (2009). new england journal of medicine, 361(15), 1475-1485	28
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