# Regulatory Role of ECM Biophysical Signals on Cell and Nuclear Mechanics: A Bibliometric and Visualized Study

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**Abstract.** Bibliographic and visualization tools can be used to reveal information from a massive amount of literature data. A bibliographic search of original articles published in English in the Web of Science Core Collection (2013–2022) using the terms extracellular matrix (ECM), cell mechanics, and nuclear mechanics. We conducted a bibliometric analysis upon which we reviewed their focus, summarized present research, and identified trends in academic research using the Bibliometrix package in R Software and CiteSpace software. In this study, we examined the current state of collaborative research on the regulatory role of ECM biophysical signals in cell and nuclear mechanics. We also examined the top 20 authors to gauge their influence. An analysis of dual maps was also used to reveal the connections among several disciplines. Moreover, the historical direct citation network revealed how the content of such research changed over time. Furthermore, disciplinary burst analysis has highlighted the evolution of ECM biophysical signals in cell and nuclear mechanics studies over the past few years, while keyword density visualization has been used to pinpoint research hotspots. Researchers can utilize these results as a guide to explore topics or concentrate on a particular area of study.

**Keywords:** Extracellular matrix, cell mechanics, nuclear mechanics, bibliographic search, citation network.

## 1. Introduction

The composition, structure, and mechanical properties of the extracellular matrix (ECM) are determined by cells during development. The ECM is essential for the formation and function of soft connective tissues. Over the past two decades, the ECM has been found to influence numerous cellular functions, such as expansion, growth, proliferation, migration, differentiation, and survival [1]. ECM mechanics must be sensed and regulated by the cells to maintain mechanical homeostasis. Mechanical homeostasis refers to the maintenance of tissue-level structural and functional integrity. Three constituents of ECM are important for its mechanical properties: elastic fibers, fibrillar collagens, glycosaminoglycans (GAGs), and proteoglycans (PGs). It is important to remember that mechanical homeostasis involves more than just collagen and elastin that support and transmit loads within the ECM; it also includes integrins, which connect extracellular and intracellular structures, and their linking proteins (such as talin and vinculin) that connect the receptors to the cytoskeleton. Moreover, the cytoskeleton comprises actin filaments, myosins, and other proteins that transmit mechanical signals. Previously, most investigators believed that ECM played a role in maintaining biological organizational integrity and physical support [2]. An important study examined the responses of cells to mechanical properties of an adhesion substrate and found that treatment of cells on firm substrates with myosin inhibitors could reduce both vinculin and phosphotyrosine at adhesion sites. Therefore, the ECM may participate in cellular interactions with the surrounding environment [3]. Since then, numerous studies have shown that the ECM has a profound impact on development, homoeostasis, fibrosis, and cancer through the discovery of ECM regulatory mechanisms [4–7]. Furthermore, measuring biophysical signals in cell mechanics and nuclear mechanics have gradually improved and deepened ECM research. However, many questions still need answers. Over the last two decades, the number of publications related to ECM has steadily increased worldwide. Therefore, ECM research progress and development trends must be analyzed comprehensively.

Bibliometrics is a quantitative and qualitative approach to analyzing specific literature through mathematics and statistics. It is effective as an objective tool for analyzing the status quo of a subject area and assessing its development. Scientific publications are typically used as the basis for creating interactive visual representations of complex biological structures. It is difficult and time-consuming for researchers to read a large amount of literature and quickly understand the state of a new research field. To address this issue, bibliometrics can quickly analyze a large body of literature and identify developments and dynamics in the field of interest to researchers through a variety of visualization tools. Tools for visual analysis of bibliometric data include CiteSpace software [8], VOS Viewer software [9], HistCite software [10], and DIVA software [11]. These tools can be used to analyze information, such as countries, author institutions, journals, collaborations, citations, and keyword evolution. Different software tools focus on different data and have different limitations; for example, the VOS Viewer software can visualize a map of basic elements, such as countries, research institutions, journals, and authors. However, the program cannot analyze the correlations between these elements. Similarly, HistCite can quickly summarize the literature but cannot identify cooperative networks, co-occurrence, and co-citation. The software used in this article is CiteSpace, which has the advantage of being able to identify research frontiers, emerging trends, and key points.

Several reviews have demonstrated that the ECM plays a key role in cellular biology and mechanics. However, a systematic bibliometric analysis of ECM research and hotspots does not exist, nor does one exist that adequately characterizes the interactions between cell function and ECM mechanisms. This study used CiteSpace to analyze the latest developments in ECM research and provide an intuitive visualization of current trends.

## 2. Materials and Methods

### 2.1. Data Source and Methods

The Science Citation Index (SCI) and Science Citation Index Expanded (SCI-E) databases were used for bibliometric analyses. The English literature database was searched using the topic search strategy from January 1, 2003, to June 1, 2022. The search terms were “extracellular matrix (ECM),” “cell mechanics,” and “nuclear mechanics.” A total of 1896 documents were retrieved and subjected to bibliometric analysis. These documents included 1,548 articles, 235 reviews, nine conference abstracts, four editorial materials, one letter, and 99 proceedings papers. Figure 1 illustrates the four-step filtering process.

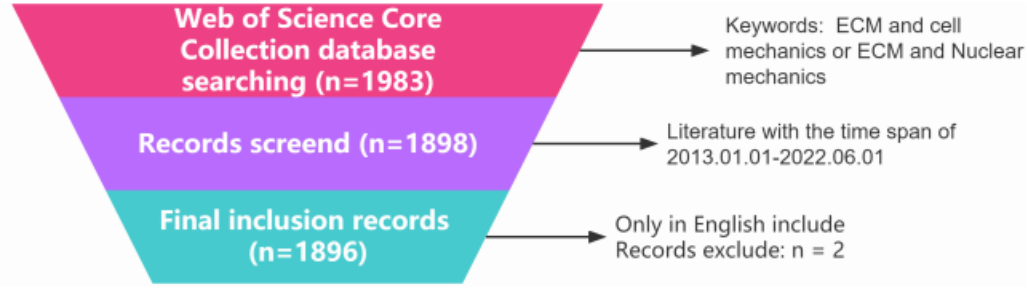


**Figure 1.** Data selection process

We employed several approaches to highlight the bibliographic data. Because their respective reflection of productivity and influence, we chose productions and citations as our leading bibliometric indicators [12]. Additionally, we incorporated other common measuring tools, such as research collaborations between countries and institutions, top contributors of journals, authors, countries, institutions, and historical direct citation networks [13–15]. We also conducted a dual-map analysis to show the relationships between various disciplines. For analysis, we added files in BibTex and plain text formats into R Studio and CiteSpace (versions 4.0.3.1 and 5.7. R5W, respectively) [16]. We used the R package bibliometrix to obtain basic information, including yearly scientific growth trends of production and publication, density visualization, keyword frequency, cooperation among

nations and production of individual nations, analysis of institutions, outstanding authors' achievements over time, and the historical direct citation network [16]. In addition, CiteSpace was applied to perform dual-map overlays depicting the correlation between disciplines in the field of ECM biophysical signals on cells and nuclear mechanics and to conduct burst disciplines in the research area between 2013 and 2022.

## 3. Results

### 3.1. Annual publication trend

From 2003–2022, we analyzed publications in the field of ECM biophysical signals in cell and nuclear mechanics. The annual publication volume has increased over the past 20 years (Figure 2A). Between 2003 and 2012, the number of publications steadily increased as ECM was used in biological detection and analysis. Beginning in 2014, more than 100 articles have been published every year for the last eight years. From 2012–2021, the number of publications has grown exponentially from 64 to 212. This may be because the application of 3D media accelerated the progress of ECM-related in vitro experiments. In the first half of 2022, 94 articles have already been published, and we estimate that more than 250 articles will be published in 2022. The annual increase in articles published each year indicates that ECM is an active research field that has drawn wide attention. According to the logistic regression model, this field is experiencing rapid publication growth (Figure 2B).

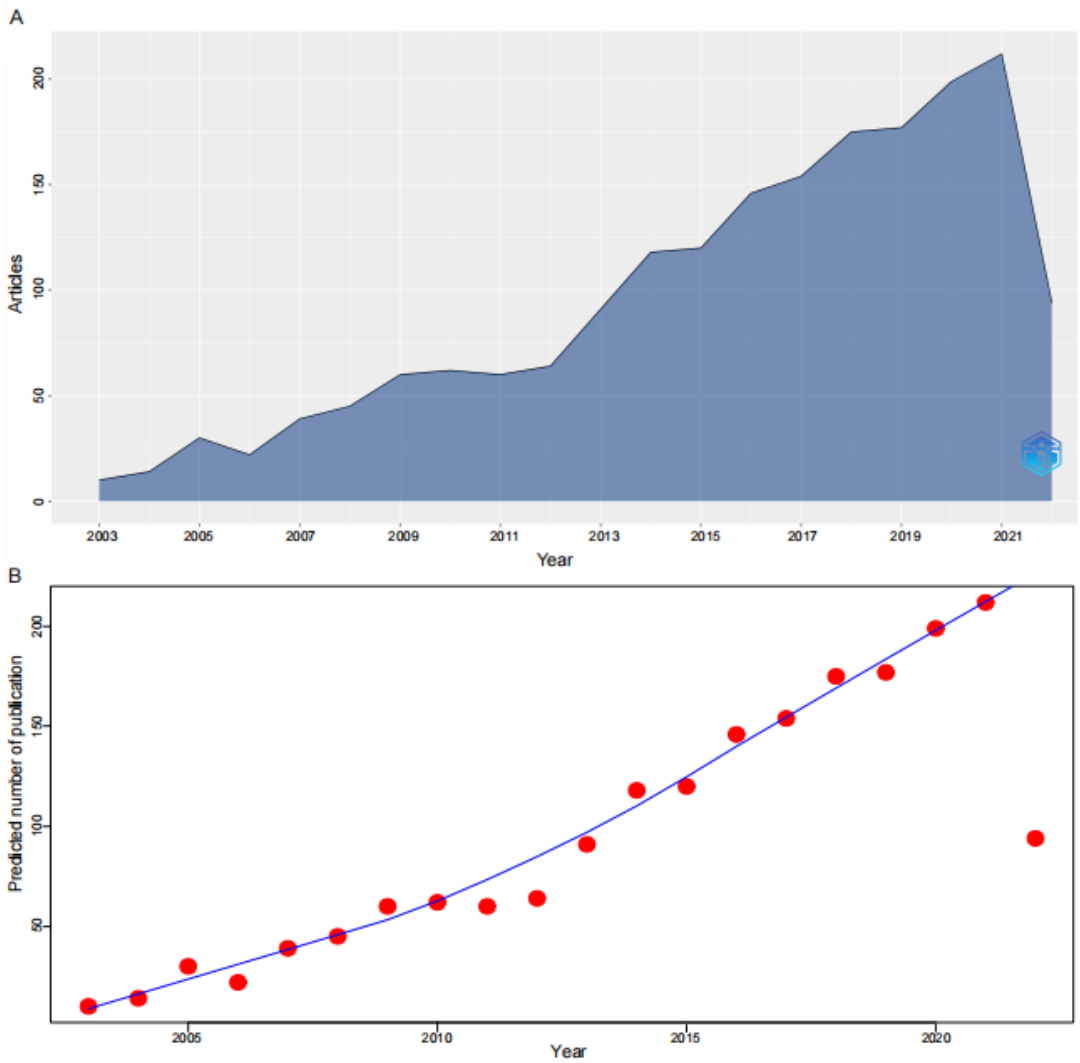


**Figure 2.** Publication trends during 2003 and 2022. (A) Annual publication volume and (B) Curves of growth trends

### 3.2. Distribution and Cooperation of Nations and Organizations

Using R software, a blue-code world map was created based on data publication country of origin (Figure 3). These documents featured 39 countries, and there were 378 collaborations between these countries. Among these, the USA and China had the highest collaboration frequency of 79.

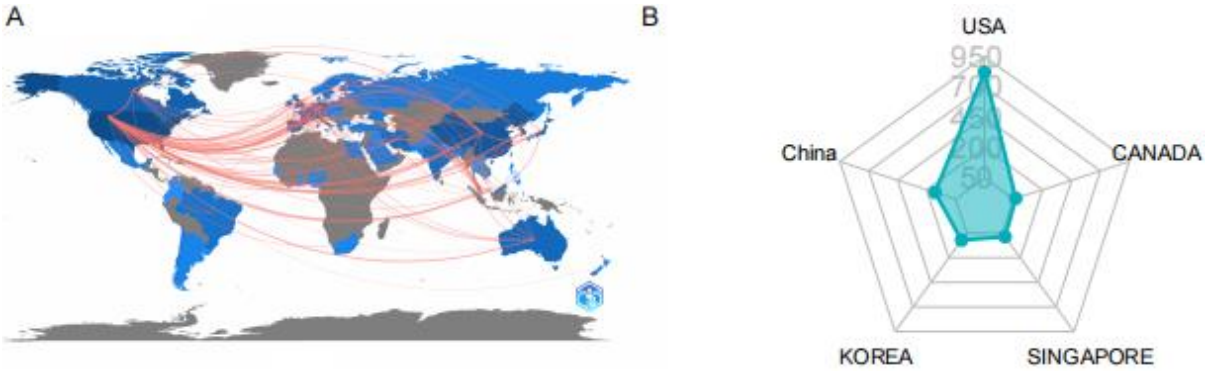


**Figure 3.** International collaboration and countries' production.(A) International collaboration world's map and (B) radar map of countries' publication.

This field has been published most frequently in the following five countries: USA (834), China (210), Korea (114), Singapore (83), and Canada (68) (Table 1 and Figure 3B).

**Table 1.** Top 20 productive countries and their total and average citations concerning regulatory role of ECM biophysical signals on cell and nuclear mechanics

| Country | Production(articles) | Total citations | Average citations |
|---|---|---|---|
| USA | 834 | 40259 | 48.27 |
| CHINA | 210 | 4575 | 21.79 |
| KOREA | 114 | 4792 | 42.04 |
| SINGAPORE | 83 | 7070 | 85.18 |
| CANADA | 68 | 1738 | 25.56 |
| GERMANY | 55 | 1702 | 30.95 |
| ITALY | 53 | 1345 | 25.38 |
| UNITED KINGDOM | 49 | 1276 | 26.04 |
| JAPAN | 48 | 1093 | 22.77 |
| IRELAND | 47 | 1513 | 32.19 |
| SPAIN | 33 | 683 | 20.7 |
| IRAN | 30 | 342 | 11.4 |
| FRANCE | 27 | 984 | 36.44 |
| INDIA | 24 | 529 | 22.04 |
| AUSTRALIA | 23 | 588 | 25.57 |
| SWITZERLAND | 22 | 1145 | 52.05 |
| ISRAEL | 21 | 474 | 22.57 |
| NETHERLANDS | 21 | 467 | 22.24 |
| BELGIUM | 16 | 297 | 18.56 |
| PORTUGAL | 12 | 170 | 14.17 |

The USA had the highest number of articles published, accounting for 44.94% of the total, much higher than the second-ranked China (210 articles), indicating that the USA dominated the field of biophysical signals in the ECM of cells and nuclear mechanisms in terms of total publications.

Regarding citations, the most cited studies were from the USA (40259), Singapore (7070), Korea (4792), China (4575), and Canada (1738) (Table 2 1). Singapore publishes many articles, yet these articles had the highest average article citations, which indicated that their studies had extensive influence in this ECM research area. In contrast, as the country with the second largest number of

published papers, China's average article citations were much lower. This may serve as a reminder to improve not only the research quantity but also research quality.

Based on analysis results, a total of 1934 research institutions were listed. The top five institutions with the highest number of publications in this field are the National University of Singapore (251), University of Pittsburgh (159), University of Michigan (157), University of Pennsylvania (126), and Trinity College Dublin (116) (Figure 4A). Additionally, there are eight American institutions in the top ten of publishing organizations, which further illustrates the USA's dominant position in this field. Figure 4B shows the cooperative relationships between the institutions. Forty-seven institutions were identified and 15 clusters were depicted, each with a different color. The purple cluster had 10 nodes, making it the largest cluster. It is dominated by institutions mainly from the United States, including Johns Hopkins University, University of Pennsylvania, and Harvard University.

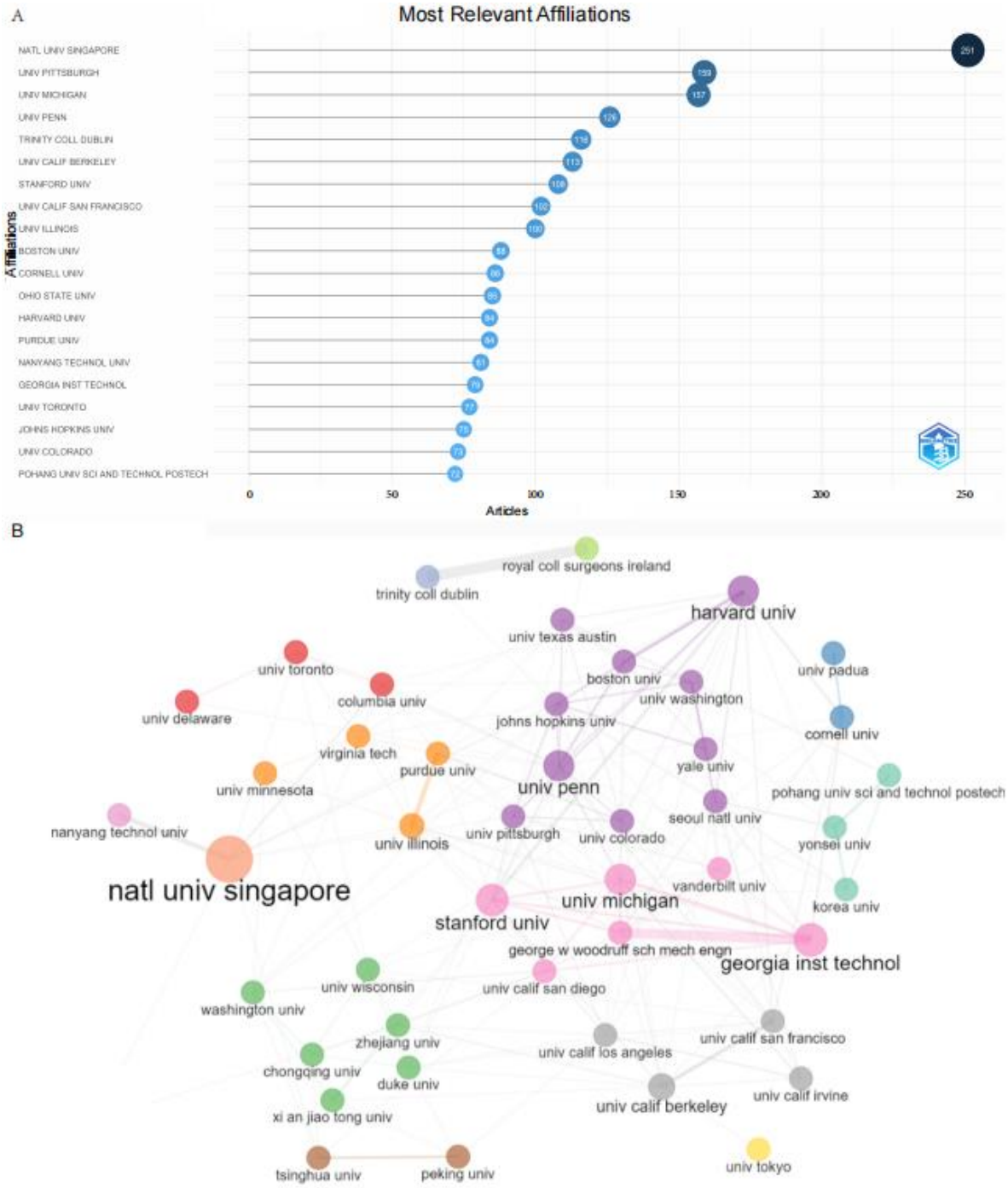


**Figure 4.** The analysis of institutions. (A) the publication volume of institutions and (B) Institution collaboration graph.

Cluster number two is pink with six nodes, most of which are also from the USA, led by Stanford University and University of California San Diego. Node size indicates article publication, whereas edge thickness represents collaboration strength. Considering the cooperative relationship between these universities, institutions with the most publications have a closer relationship.

### 3.3. Top Authors' Production over Time

Author influence is determined by the number of research articles published and citation frequency. The higher the number of published articles and citation rate, the more authoritative the authors are in the field. The most influential 20 authors in the field are represented by node size, indicating publication number, and color depth indicates the number of attributed citations per year (Figure 5). Our analysis of both the published number and citations over time reveals that the majority of the top 20 authors are American and Singaporean scholars, which further implies that USA and Singaporean scholars have high influence in the ECM field. Additionally, over 100 articles were published by the top 9 scholars. The most influential in this field is Professor Ramakrishna S. from the National University of Singapore, who has published 30 articles. His research areas included developing nanofibers and three-dimensional bioinks based on alginate for biomedical applications. His latest article, titled **"**Electrospinning for tissue engineering applications" was published in Progress in Materials Science in 2021 and has been cited 108 times. In this study, researchers mimicked the ECM by engineering structures that provided oxygen and nutrients to the tissue and removed metabolic waste during tissue regeneration.

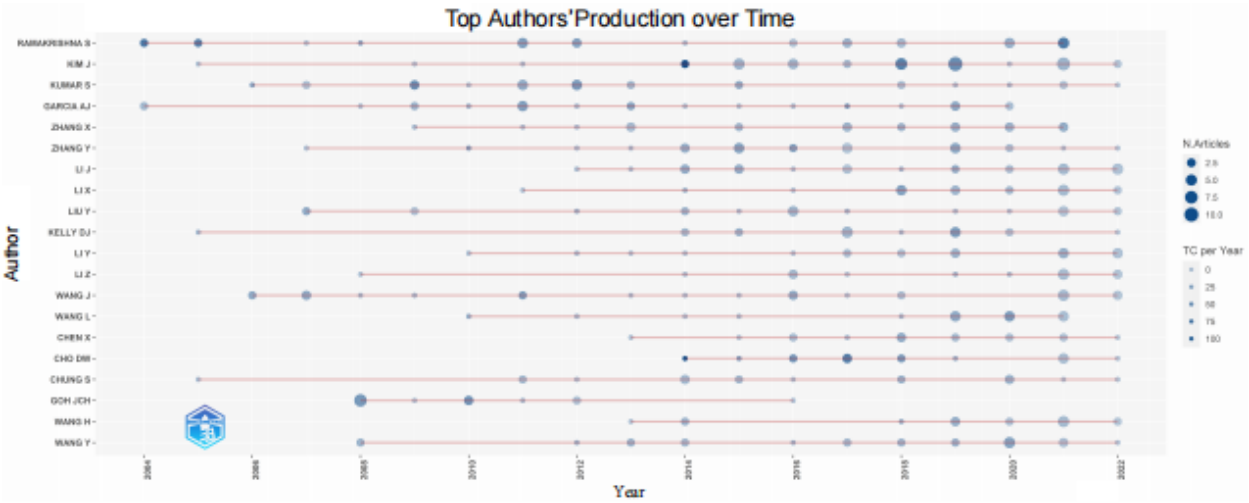


**Figure 5.** Top 20 authors' production over time.

### 3.4. Journal Source

Based on this field's publication volumes, we ranked the top 20 journals (Table 2). A total of 102 publications were published in *Biomaterials*, followed by 64 publications in *Acta Biomaterialia*. *Biosensor and Bioelectronics* has the highest CiteScore (20.1) and the highest impact factor (15.304 in 2022) with an h-index of 381. This journal focuses on research involving biosensors and bioelectronics, which are favored by most scientists for their research, design, development, and application. *Acta Biomaterialia* has also been recognized by scholars in ECM for 64 articles.

**Table 2.** Top 20 most productive and impact journals concerning regulatory role of ECM biophysical signals on cell and nuclear mechanics

| Journal | H_index | Total citation | Publication(articles) |
|---|---|---|---|
| Biomaterials | 53 | 9062 | 102 |
| Acta Biomaterialia | 28 | 2470 | 67 |
| Proceedings of the National Academy of Sciences of The United States of America | 28 | 3448 | 32 |
| Plos One | 19 | 1068 | 36 |
| Journal of Biomedical Materials Research Part A | 17 | 1603 | 24 |
| Scientific Reports | 17 | 909 | 45 |
| Annals of Biomedical Engineering | 15 | 1040 | 22 |
| Integrative Biology | 14 | 1149 | 19 |
| Journal of Biomechanics | 14 | 907 | 24 |
| Tissue Engineering Part A | 14 | 826 | 19 |
| Acs Biomaterials Science \& Engineering | 12 | 439 | 38 |
| Advanced Healthcare Materials | 12 | 443 | 24 |
| Biomechanics And Modeling in Mechanobiology | 12 | 946 | 17 |
| Biophysical Journal | 12 | 1043 | 18 |
| Biotechnology And Bioengineering | 12 | 622 | 18 |
| Journal of Cell Science | 12 | 1201 | 14 |
| Acs Applied Materials \& Interfaces | 11 | 454 | 18 |
| Journal Of Biomechanical Engineering-Transactions of The Asme | 11 | 429 | 22 |
| Journal of Materials Chemistry B | 11 | 347 | 14 |
| Journal Of the Mechanical Behavior of Biomedical Materials | 11 | 527 | 26 |

### 3.5. Analysis of discipline association based on dual-maps

A bipartite overlay is a visual analysis method in which two maps are superimposed. The former is called an overlay map, and the latter is called a base map. Map overlays and result comparisons can provide insights into the data sources [17–20]. In the dual-map overlay method, more than 10,000 cited journals in the Web of Science (WoS) database were used as the base map for the bipartite overlay analysis. The overlay map was derived from the cited literature data, showing how the research topics are related overall on a dual map [21–23]. Thus, dual-map overlays provide a broader view of content evolution at the discipline level. Our study generated a journal map option based on Journal Citation Reports for CiteSpace overlays. By using the "add overlay" command, one can overlay tumor-related macrophage research data on the original base map, and the associations between disciplines in tumor-related macrophages research are made visible (Figure 6). The left side of Figure 6 shows the status of tumor-related macrophage research in the disciplines cited, whereas the right-side displays tumor-related macrophage research by discipline according to the cited literature's author. This research is linked by a wave-shaped curve [24]. There are two areas: "physics, materials, chemistry" on the left and "chemistry, materials, physics" and "molecular, biology, genetics" on the right. The published papers were mostly developed in the left-hand area but were largely affected by the right-hand area. Citations follow three main trails, depicted as green and orange curves highlighted with journal tags.

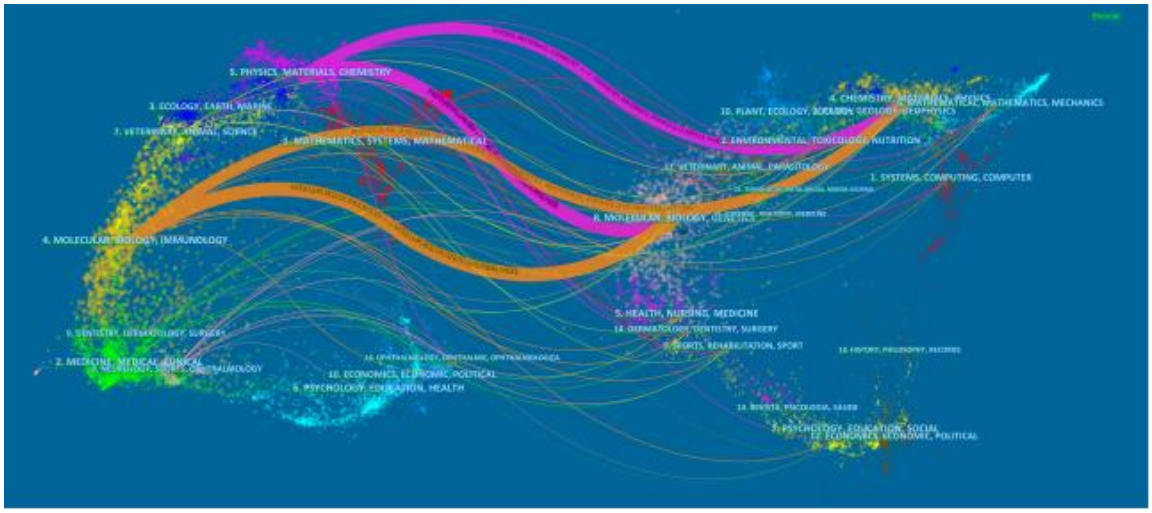


**Figure 6.** A dual-map overlay showing the correlation between disciplines in ECM research.

### 3.6. The Strongest Citation Bursts of New Disciplines

Table 3 depicts the discipline types from 2013–2022 related to the field of the regulatory role of ECM biophysical signals on cell and nuclear mechanics. According to this information, this field experiences bursts of new disciplines about every year on average (Table 3).

**Table 3.** Burst disciplines in the field of TAMs during 2013 and 2022.

| Subject Categories | Year | Strength | Begin | End | 2003 - 2022 |
|---|---|---|---|---|---|
| CONFERENCE PROCEEDINGS CITATION INDEX - SCIENCE (CPCI-S) | 2003 | 7.27 | **2003** | 2009 | |
| CELL & TISSUE ENGINEERING WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED) | 2003 | 5.71 | **2003** | 2006 | |
| ENGINEERING, BIOMEDICAL WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED) | 2003 | 7.59 | **2004** | 2010 | |
| BIOPHYSICS | 2003 | 5.44 | **2006** | 2010 | |
| ENGINEERING | 2003 | 3.88 | **2008** | 2009 | |
| ORTHOPEDICS WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED) | 2003 | 3.81 | **2017** | 2019 | |
| NANOSCIENCE & NANOTECHNOLOGY | 2003 | 4.85 | **2019** | 2022 | |
| CHEMISTRY, MULTIDISCIPLINARY | 2003 | 3.49 | **2019** | 2020 | |
| ONCOLOGY WE SCIENCE CITATION INDEX EXPANDED (SCI-EXPANDED) | 2003 | 3.63 | **2020** | 2022 | |

However, emerging disciplines are brief in duration. Among them, cell and tissue engineering has lasted the longest, approximately seven years. With increased developments, tissue bioengineering specialists have become more interested in this field. In the last three years, oncology has emerged as a novel discipline because cancer research has focused on the role of ECM physical properties, especially the robust tumor microenvironment and metastasis. Several studies have confirmed that integrins can promote tumorigenesis and development by activating downstream pathways and stiffening the ECM. The main mechanism of action for this change is ECM remodeling, ECM deposition, fiber arrangement, and crosslinking. We can also increase research rate in this field by integrating the hotspots according to Table 3.

### 3.7. Keywords analysis

Research hotspots can be identified through keyword cooccurrence, whereas cutting-edge topics can be identified using burst keywords. By analyzing the keyword distribution, we can identify research hotspots and cutting-edge topics. As presented in Figure 7, the keywords included in vitro differentiation, stiffness, adhesion, expression, collagen, mechanical properties, mechanics, tissue, growth, cells, mechanotransduction, and proliferation. We manually removed some non-specific words and screened meaningful keywords, including stiffness, collagen, mechanical properties, and mechanotransduction.

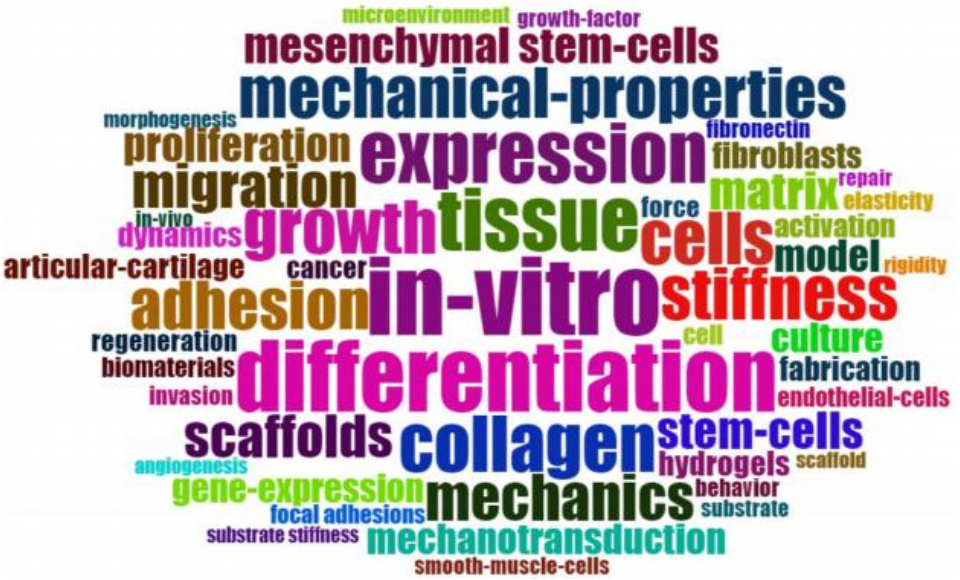


**Figure 7.** The keywords' analysis.

## 4. Discussion

Using its content, 31 articles were screened to determine whether they were related to ECM, 18 of which were reviews and 13 were articles. We reviewed this based on highly cited articles and keywords identified during our literature search. We have provided the most highly-cited and current information available concerning ECM biophysical signals affecting cell and nuclear processes.

### 4.1. ECM mechanics and viscoelasticity

Most organic objects and human tissues appear solid, but they do not behave as solids when compressed or subjected to tensile forces. They are generally elastic, meaning that under compression or strain they return to their previous form. However, if sufficient strain is applied, these organic objects will become permanently deformed; this is called inelastic deformation. Unlike solid objects, the ECM does not deform in the same manner but instead deforms and gradually returns to its former shape. This property is termed "viscoelasticity," and viscoelastic objects are intermediate between liquids and solids. They exhibit an elastic response in the short term, like elastic solids, and a viscous response in the long term, such as viscous liquids. Therefore, the ECM exhibits a high degree of viscoelasticity. In a review published in *Nature*, viscoelastic materials exhibit both in-phase responses, storing the external force elastically, and out-of-phase responses where it loses its shape [25]. The Young's modulus of biological soft tissue is an important relationship to remember in this context, that there exists a point where further strain fractures or permanently distorts an object. The occurrence of many diseases can cause changes in the vasoelasticity of biological soft tissue. Thus, changes in vasoelasticity may be able to predict local lesion occurrence. These changes can be assessed by generating a force-deformation curve by measuring the deformation of soft tissue under different strains. The loss modulus of soft tissue is about 10–20% of the storage modulus [26]. Hard tissues, such as bone and cartilage, are also viscoelastic with a reported loss modulus of approximately 10% of the storage modulus.

The actin cytoskeleton plays a crucial role in matrix loading. Mizuno et al. measured the mechanical properties of a three-component model that consisted of myosin II, actin filaments, and cross-linkers. They found that the actin cytoskeleton exhibits viscoelasticity [27]. Fibroblasts maintain mechanical homeostasis not by projecting constant tension but by adjusting to contractile force by changing their responsive force in relation to mechanical displacement. The maintenance of this mechanical homeostasis requires actin myosin [28].

As mentioned previously, elastomers exhibit linear relationships between stress and strain, whereas ECM with viscoelastic properties exhibit nonlinear relationships between stress and strain and a linear relationship between stiffness and stress ($k = P/\delta$, where P is the constant force acting on the structure, and $\delta$ is the deformation due to the force) [29]. Short-term mechanical homeostasis is achieved through matrix reorganization and cross-linking through negative feedback. Long-term homeostasis is balanced by matrix degradation and newly deposited matrix constituents [30].

Cells regulate mechanical homeostasis by sensing changes in the ECM through feedback mechanisms that involve integrin mechanical transduction pathways. These pathways help cells sense internal and external mechanical stresses and thereby regulate the rates of ECM synthesis and degradation. Generally, weaker forces increase the matrix synthesis and contractility, whereas stronger forces induce matrix degradation and hardening. Dysregulation of negative feedback pathways or viscoelastic changes can cause various diseases. There are many examples of this phenomenon. Marfan syndrome is a multisystem disorder caused by mutations in the fibrillin 1 gene [31]. Fibrosis is a condition that occurs when there is a prolonged increase in stress/strain such that scar tissue develops [32]. Gene mutations associated with force-dependent matrix remodeling, such as TGF-β or angiotensin pathways, reduce the ECM's feedback and change the default resistance of mechanical homeostasis, which can lead to thoracic aortic aneurysms and artery dissection [33]. Importantly, tumorigenesis can be initiated by altered ECM composition or cell-ECM interactions. Sinkus et al. used magnetic resonance elastography to analyze the viscoelasticity differences between malignant and benign breast tumors [34]. Previous mammary epithelial models have been associated with increased ECM stiffness and malignant phenotypes. Other research has shown that increasing ECM stiffness alone induces malignant characteristics in normal mammary epithelium [4].

### 4.2. Regulatory role of ECM biophysical signals on cell mechanics

Fibroblasts are responsible for building and maintaining the ECM in most soft connective tissues. Fibroblasts secrete elastin, collagen, glycoproteins, and GAGs. ECM force changes are monitored and regulated by integrins that connect matrix proteins and linker proteins, such as talin and vinculin, to the cytoskeleton, actin, and non-muscle myosin. Normal cells are capable of probing substrate rigidity, and this mechanical feedback is essential for regulating cell growth and apoptosis. When cells were cultured on artificial substrates with the same chemical properties but differ in hardness, cells cultured on flexible substrates had lower rates of DNA synthesis and increased rates of apoptosis than those cultured on rigid substrates. These flexible substrates decreased both traction forces and cell-spreading areas [35]. Cell migration to areas of higher ECM rigidity is called "durotaxis," and this characteristic contributes to wound healing, immune responses, and cancer metastasis [36]. However, cell migration speed does not increase with substrate stiffness. Instead, speed varies biphasically with ECM stiffness and is highest at intermediate stiffness. The dynamic adjustment of FAK/phospho-paxillin/vinculin signaling regulates the stiffness range [37]. By sensing the external mechanical load, the ECM promotes cytoskeleton assembly into actin stress fibers and mature integrin-based focal adhesions (FAs), resulting in different signaling cascades; this is called mechanotransduction [38,39]. Integrin-based mechanotransduction first senses force transmission between the cell and ECM. Subsequently, force transmission leads to increased kinase activity and changes in protein conformation, thereby inducing an increase in integrin affinity and biochemical signals to produce cellular responses, such as cell migration or differentiation [40].

Integrins play an important role in the process of mechanotransduction. Integrins are transmembrane receptors that link the extracellular matrix to the intracellular actin skeleton. Integrins are heterodimers of α- and β-subunits, and there are 24 different integrin receptors in mammals, each of which recognizes a specific set of ECM ligands [41]. After binding to their specific ligand, integrins recruit proteins to their short cytoplasmic tail, on which different adhesion structures assemble that differ in protein composition, function, and mechanical properties.

The molecular clutch refers to this dynamic mechanical connection between ECM-bound integrins and the actomyosin cytoskeleton. The molecular clutch determines the direction of cell migration, in

which talin plays an important role. Talin directly activates F-actin and integrin activation in the cytoplasm, and vinculin increases F-actin and talin binding. When integrin FAs are not connected to actomyosin, the cell cannot move owing to the molecular clutch not being engaged. However, when integrin FAs are linked to actomyosin, the molecular clutch is initiated, which causes the linker proteins talin and vinculin to unfold and thereby alter protein interactions and signaling [42–45]. The integrin adhesome both recruits' different proteins to FAs and forms a dynamic interaction network, in which intracellular and extracellular factors cooperate during mechanical movement. This network leads to protein conformational changes that cause stretching, compression, or cell displacement. In conclusion, the matrix-integrin-cytoskeleton system plays an important role in regulating biophysical processes. This biophysical phenomenon is particularly evident in rigid substrates. Conversely, a flexible matrix inhibits actin cytoskeleton because of its by matrix deformation, which decreases cell adhesion and reduces the loading rate [43,46].

Relating to cell movement, mechanotransduction is the process by which cellular responses are produced by mechanical means and involves many gene expression changes and signaling pathway activations. Mechanotransduction produces different cell responses at different time points. Both short- and long-term transduction require integrin-dependent RhoA signalling and downstream actin dynamics. By altering RhoA signaling, cells regulate proliferation and differentiation in response to ECM stiffness level, which changes cell shape and density. The downstream pathway of RhoA is critical for transmitting ECM signals. For example, increased ECM stiffness results in proliferation and transformation of mammary epithelial cells into invasive phenotype. ECM regulation of cell proliferation and differentiation is mediated by YAP/TAZ [47,48]. In addition, studies have shown that myocardin-related transcription factors and the nuclear LINC complex are involved in the connection between the cytoskeleton and nuclear skeleton [49,50]. Guilluy et al. reported that mechanical stretching of integrins activates FAK and Src family tyrosine kinases and identified two guanine nucleotide exchange factors (GEFs), including LARG and GEF-H1. LARG is activated by the Src family tyrosine kinase Fyn, and GEF-H1 is enhanced by ERK downstream of FAK and Ras signaling cascades [51].

## 5. Conclusion

An in-depth bibliometric analysis of ECM literature was performed in this study, which produced visual representations based on research status, historical development, and the growing tendencies in the ECM field between 2013 and 2022. Research on the ECM continues to grow, and the main contributors to the field are noted in this study. This paper also discusses how recent research focuses on the complex biochemical and biophysical characteristics of the ECM and how ECM viscoelasticity influences cellular behavior. Moreover, the future research will likely focus on the pathways through which tissues maintain normal stromal organization and feedback regulation. Other focuses likely will be animal model design to elucidate the therapeutic potential of targeting signaling events downstream of mechanotransduction for treating diseases and for tissue regeneration. Readers who do not have extensive background knowledge of this topic will benefit from this article by gaining an understanding of this recent research.

Supplementary Materials: Not applicable.

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