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Landmark Studies in Cell Morphology: A Bibliometric Analysis*

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Основные исследования в области морфологии клеток: библиометрический анализ

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Introduction. Cell morphology has been a crucial area of study since the invention of the microscope, evolving significantly with the advancement of ultramicroscopic techniques. This study analyzes the top 100 most cited publications on cell morphology to uncover key research trends and influential works from the past three decades.

Актуальность. Морфология клеток остается важнейшей областью исследования с момента изобретения микроскопа, получив значительный импульс к развитию с внедрением ультрамикроскопических методов. В данной работе представлен анализ 100 наиболее цитируемых публикаций по морфологии клеток, выполненный с целью

* The article contains an online application that contains additional materials.

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Materials and Methods. A bibliometric analysis was conducted using the Web of Science Core Collection database, covering articles published from January 1985 to April 2023. From an initial pool of 1,251,024 articles, the top 100 most cited publications were identified. Data on publication year, citation counts, journals, authors, geographical distribution, institutions, and keywords were extracted. VOSviewer and Bibliometrix were used for statistical analysis.

Results. The top 100 articles were published in 43 journals, including high-impact publications such as *Nature, Science*, and *Cell*. The most cited article, "Matrix Elasticity Directs Stem Cell Lineage Specification," had 9,832 citations. The United States contributed 70 articles. Key research themes identified included the mechanical microenvironment, stem cell research, and advanced imaging techniques.

Conclusion. This study highlights the importance of the extracellular matrix and signaling pathways in determining cell morphology. It underscores the predominant role of high-impact journals and emphasizes the need for multidisciplinary approaches in future research on cell morphology.

Keywords: cell morphology; bibliometric analysis; extracellular matrix; imaging technology; cell behavior

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определения ключевых тенденций в исследованиях за последние три десятилетия и выявления наиболее значимых работ в данной области.

Материалы и методы. Библиометрический анализ выполнен с использованием базы данных Web of Science Core Collection, в которую включены статьи, опубликованные в период с января 1985 по апрель 2023 г. Из первоначальной выборки, состоявшей из 1 251 024 публикаций, были отобраны 100 наиболее цитируемых статей. Были извлечены следующие данные: год публикации, количество цитирований, журналы, авторы, географическое распределение, учреждения и ключевые слова. Для статистического анализа и визуализации данных применялись программы VOSviewer и Bibliometrix.

Результаты. 100 наиболее цитируемых статей были опубликованы в 43 журналах, включая издания с высоким импакт-фактором, такие как Nature, Science и Cell. Наиболее цитируемая работа, «Matrix Elasticity Directs Stem Cell Lineage Specification», получила 9832 цитирования. Авторы из США внесли вклад в размере 70 статей. Ключевыми темами стали изучение механических свойств микроокружения, исследования стволовых клеток и передовые методы визуализации.

Выводы. Настоящее исследование подчеркивает ключевую роль внеклеточного матрикса и сигнальных путей в определении морфологии клеток. Работа также демонстрирует доминирующую роль журналов с высоким импакт-фактором в данной области и указывает на необходимость применения междисциплинарных подходов в будущих исследованиях клеточной морфологии.

Ключевые слова: морфология клеток; библиометрический анализ; внеклеточный матрикс; технологии визуализации; поведение клеток

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Introduction

Cell morphology observation began with the invention of the microscope [1], leading to the gradual description of various human cells and tissues [2]. The advancement of ultramicroscopic techniques further enhanced the understanding of cell morphology and ultrastructure [3]. Given the close relationship between cell morphology, intracellular ultrastructure, cell function, and cell fate, the study of cell morphology holds significant value.

Cells undergo multilevel activation, motility, and response events both in vivo and in vitro, ultimately achieving a quasi-equilibrium morphology linked to their functional state. These states include fundamental cellular processes such as proliferation, adhesion, apoptosis, migration, and differentiation [4-6]. Cell morphology, in turn, revealed critical insights into cell function, treatment responses, resistance, and signaling pathway activation. In breast cancer research, single-cell morphology encodes the molecular, migratory, and biophysical architecture of cancer cells, exhibiting specific alterations in osteotropic phenotypes [7]. Such morphological analyses were widely applied in various aspects of cancer research, including diagnosis, prognosis estimation, treatment decision-making, and evaluation of treatment responses [8, 9, 10]. For instance, in the diagnosis and prognosis prediction of hematopoietic system diseases, chromosome karyotype and molecular features played pivotal roles. In chronic myeloid leukemia, peripheral blood smears and bone marrow biopsy results reveal increased myeloid cells with high nuclear-cytoplasmic ratios, irregular nuclear contours, and prominent nucleoli, providing essential diagnostic information [11].

With increasing interest in the relationship between cell morphology and cell function, high-content imaging [12], image processing [13, 14], and algorithms [15] have greatly progressed. This enhanced imaging capability has particularly advanced our understanding of nanoscale features of cellular structures and morphology. For instance, recent studies using these advanced imaging methods have demonstrated that changes in mitochondrial structures actively participate in programmed cell death

[16, 17] and influence membrane morphological structure changes [18]. The morphology-phenotype connection has been previously summarized; several studies suggest that changes in cell shape influence cell state through mechanotransduction and nuclear changes [19].

Bibliometrics was extensively employed across various disciplines to pinpoint significant publications and assess research trends. It analyzed metrics such as citation counts, publication years, authorship, journals, and keywords to provide insights into the research dynamics and developmental trajectories within a particular field. For instance, Li et al. analyzed the top 100 most cited papers on bone metastasis and uncovered key research hotspots and future directions [20]. This method not only highlighted the most influential studies within a field but also aided researchers in identifying potential collaborators and charting future research paths [20, 21].

This study examined the top 100 most cited publications in cell morphology, offering an in-depth analysis of their quality and impact. It highlighted pivotal milestones and emerging research directions over the past three decades. By exploring these influential studies, the review provided valuable insights into the evolving trends and current research hotspots in the field, thereby guiding future advancements and encouraging continued innovation in cell morphology research.

Material and Methods

Data source and search strategy

The Web of Science (WOS) database, available at http://apps.webofknowledge.com, is the world's largest citation database. It includes nearly 9,000 authoritative journals and helps evaluate the academic significance of articles in specific fields. Relevant articles from the Web of Science Core Collection (WoSCC) were searched and exported on April 16, 2025. The search strategy employed was [TS (topic search) = (morphology OR shape OR component OR structure OR architecture OR cytoarchitecture OR cytomorphology OR cytoshape) AND (cell OR cellular)]. To facilitate further analysis, only original articles and reviews written in English were included. This search yielded a total of 1,251,024 articles, which were ranked in descending order of citation frequency. A full record and cited references were then exported from WoSCC in plain text format. For preliminary literature screening, the top 2,000 cited articles were downloaded. From these, the top 100 cited records specifically focused on cell morphology were identified from the top 1,600 cited articles. Any disagreements during the selection process were resolved by discussion until a consensus was reached. The flowchart of data collection and analysis is shown in Figure S1 (see online appendix).

Data extraction

After identifying the top 100 most-cited articles, all pertinent details were sourced from the WoSCC. These details included the article's title, citation count, citation density, year of publication, authorship, contributors, publishing journal, PMID, and other relevant information. Citation density was manually calculated as the average number of citations received per year since the publication of each work.

Statistical analysis

We employed the VOSviewer (version 1.6.17) to integrate author countries, contributing institutions, and to visualize keyword mapping. In the visual maps generated, various nodes represented authors, nations, institutions, and keywords. The size of each node indicated the volume of associated references or citations, while the connections between nodes represented collaboration and co-occurrence relationships. Different colors were assigned to nodes and links to denote clusters and various attributes. To further analyze bibliographic information and create visualizations, we used the Bibliometrix package (version 4.1.4) in R (version 4.3.3). The Biblioshiny app, a graphical web interface within the RStudio environment (RStudio version 2023.12.1+402 "Ocean Storm"), was also utilized to streamline the visualization process. Descriptive statistics for year of publication, number of citations, citations per year, authors, country, organization, journal, and impact factor (IF) of journal (based on the 2022 science edition of the Journal Citation Reports (Thomson Reuters, New York, NY, USA)) by the Microsoft Excel 2016 software.

Result

Article analysis

A total of 1,264,465 articles were obtained from January 1985 to April 2025. Among these, 1,251,024 articles were written in English. The top 100 articles were included based on the number of citations and were displayed in the Tab. 1. The most cited article, "Matrix Elasticity Directs Stem Cell Lineage Specification" by Engler et al., published in Cell, received 9,832 citations, averaging 578.4 citations per year. The average citations per year provided a clearer picture of an article's impact over time. "Deep Learning in Medical Image Analysis," published in 2017, averaged 324.8 citations per year, reflecting the growing importance of artificial intelligence in medical imaging. As the most recent article among the top 100 cited papers, it highlighted contemporary relevance and rapid advancements in cell morphology and AI research. The least cited article [22] (1,009 citations) is "Nanoscale Architecture of Integrin-Based Cell Adhesions" by Kanchanawong et al., published in *Nature*, with an average of 77.6 citations per year.

Table 1. List of the 100 top-cited articles

Rank	Article Title	Journal	Publication Year	Times Cited WoS Core	Average per year
1[23]	Matrix elasticity directs stem cell lineage specification	CELL	2006	9832	578.4
2[24]	Apoptosis: A review of programmed cell death	TOXICOLOGIC PATHOLOGY	2007	8230	514.4
3[25]	Rho GTPases and the actin cytoskeleton	SCIENCE	1998	5101	204.0
4[26]	Comprehensive Mapping of Long-Range Interactions Reveals	SCIENCE	2009	4732	338.0
Rank	Article Title	Journal	Publication Year	Times Cited WoS Core	Average per year
	Folding Principles of the Human Genome				
5[27]	Tissue cells feel and respond to the stiffness of their substrate	SCIENCE	2005	4627	257.1
6[28]	A bivalent chromatin structure marks key developmental genes in embryonic stem cells	CELL	2006	3883	228.4
7[29]	Topological domains in mammalian genomes identified by analysis of chromatin interactions	NATURE	2012	3875	352.3
8[30]	Cell migration: Integrating signals from front to back	SCIENCE	2003	3681	184.1
9[31]	A 3D Map of the Human Genome at Kilobase Resolution Reveals Principles of Chromatin Looping	CELL	2014	3522	391.3
10[32]	Role of YAP/TAZ in mechanotransduction	NATURE	2011	3258	271.5
11[33]	Cell shape, cytoskeletal tension, and RhoA regulate stem cell lineage commitment	DEVELOPMENTAL CELL	2004	3223	169.6
12[34]	CellProfiler: image analysis software for	GENOME BIOLOGY	2006	3218	189.3
	identifying and quantifying cell phenotypes				
13[35]	Astrocytes: biology and pathology	ACTA NEUROPATHOLOGICA	2010	3191	245.5
14[36]	Foreign body reaction to biomaterials	SEMINARS IN IMMUNOLOGY	2008	3178	211.9
15[37]	Tensional homeostasis and the malignant phenotype	CANCER CELL	2005	2802	155.7
Rank	Article Title	Journal	Publication Year	Times Cited WoS Core	Average per year
16[38]	Glutamate Receptor Ion Channels: Structure, Regulation, and Function	PHARMACOLOGICAL REVIEWS	2010	2395	184.2
17[39]	Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue	STEM CELLS	2006	2344	137.9
18[40]	Taking cell-matrix adhesions to the third dimension	SCIENCE	2001	2335	106.1
19[41]	Functional neurogenesis in the adult hippocampus	NATURE	2002	2210	105.2
20[42]	A microRNA component of the p53 tumour suppressor network	NATURE	2007	2144	134.0
21[43]	Autophagy in health and disease: A double-edged sword	SCIENCE	2004	2110	111.1
22[44]	The biology and function of fibroblasts in cancer	NATURE REVIEWS CANCER	2016	2106	300.9
23[45]	Convergence of Wnt, beta-catenin, and cadherin pathways	SCIENCE	2004	2086	109.8

24[46]	Novel cell death program leads to neutrophil extracellular traps	JOURNAL OF CELL BIOLOGY	2007	2077	129.8
25[47]	The biology of human natural killer-cell subsets	TRENDS IN IMMUNOLOGY	2001	2071	94.1
26[48]	Unmutated Ig V-H genes are associated with a more aggressive form of chronic lymphocytic leukemia	BLOOD	1999	2055	85.6
27[49]	Mechanisms of fibrosis:	NATURE	2012	2050	186.4
Rank	Article Title	Journal	Publication Year	Times Cited WoS Core	Average per year
	therapeutic translation for fibrotic disease	MEDICINE			
28[50]	Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function	NATURE MEDICINE	2001	1991	90.5
29[51]	Deep Learning in Medical Image Analysis	ANNUAL REVIEW OF BIOMEDICAL ENGINEERING, VOL 19	2017	1949	324.8
30[52]	Focal adhesion kinase: In command and control of cell motility	NATURE REVIEWS MOL CELL BIOL	2005	1914	106.3
31[53]	In vitro cytotoxicity testing of polycations: influence of polymer structure on cell viability and hemolysis	BIOMATERIALS	2003	1896	94.8
32[54]	Three-dimensional super-resolution imaging by stochastic optical reconstruction microscopy	SCIENCE	2008	1886	125.7
33[55]	Apoptosis: controlled demolition at the cellular level	NATURE REVIEWS MOL CELL BIOL	2008	1834	122.3
34[56]	Environmental sensing through focal adhesions	NATURE REVIEWS MOL CELL BIOL	2009	1828	130.6
35[57]	Close contacts with the	SCIENCE	1998	1751	70.0
Rank	Article Title	Journal	Publication Year	Times Cited WoS Core	Average per year
	endoplasmic reticulum as determinants of mitochondrial Ca2+ responses				
36[58]	Transmembrane extracellular matrix-cytoskeleton crosstalk	NATURE REVIEWS MOL CELL BIOL	2001	1744	79.3
37[59]	Structure and regulation of voltage-gated Ca2+ channels	ANNUAL REVIEW OF CELL AND DEVELOPMENTAL BIOLOGY	2000	1782	77.5
38[60]	Crystal structure of a mammalian voltage-dependent Shaker family K+ channel	SCIENCE	2005	1743	96.8
39[61]	Cell mechanics and the cytoskeleton	NATURE	2010	1727	132.8
40[62]	Effects of substrate stiffness on cell morphology, cytoskeletal structure, and adhesion	CELL MOTILITY AND THE CYTOSKELETON	2005	1722	95.7
41[63]	Mitofusin 2 tethers endoplasmic reticulum to mitochondria	NATURE	2008	1687	112.5
42[64]	Crystal structure of parallel quadruplexes from human telomeric DNA	NATURE	2002	1681	80.0
43[65]	Local force and geometry sensing regulate cell functions	NATURE REVIEWS MOL CELL BIOL	2006	1673	98.4
44[66]	The caveolae membrane system	ANNUAL REVIEW OF BIOCHEMISTRY	1998	1648	65.9

Rank	Article Title	Journal	Publication Year	Times Cited WoS Core	Average per year
45[67]	Cells lying on a bed of microneedles: An approach to isolate mechanical force	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	2003	1550	77.5
46[68]	Mesenchymal stem cells reside in virtually all post-natal organs and tissues	JOURNAL OF CELL SCIENCE	2006	1541	90.6
47[69]	X-ray structure of a voltage-dependent K+ channel	NATURE	2003	1530	76.5
48[70]	Morphogenesis and oncogenesis of MCF-10A mammary epithelial acini grown in three-dimensional basement membrane cultures	METHODS	2003	1517	75.9
49[71]	The 26S proteasome: A molecular machine designed for controlled proteolysis	ANNUAL REVIEW OF BIOCHEMISTRY	1999	1508	62.8
50[72]	Role of target geometry in phagocytosis	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	2006	1484	87.3
51[73]	Control of Stem Cell Fate by Physical Interactions with the Extracellular Matrix	CELL STEM CELL	2009	1413	100.9
52[74]	Nanomechanical analysis of cells from cancer patients	NATURE NANOTECHNOLOGY	2007	1396	87.3
53[75]	Geometric cues for directing the differentiation of mesenchymal stem cells	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	2010	1346	103.5
54[76]	Regulation of the small GTP-binding protein Rho by cell adhesion and the cytoskeleton	EMBO JOURNAL	1999	1337	55.7
55[77]	Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA	1999	1332	55.5
56[78]	Structural determinants of water permeation through aquaporin-1	NATURE	2000	1329	57.8
57[79]	The role of dynamin-related protein 1, a mediator of mitochondrial fission, in apoptosis	DEVELOPMENTAL CELL	2001	1317	59.9
58[17]	Mitochondrial fusion and fission in cell life and death	NATURE REVIEWS MOL CELL BIOL	2010	1316	101.2
59[80]	Mitochondria: More than just a powerhouse	CURRENT BIOLOGY	2006	1313	77.2
60[81]	A tense situation: forcing tumour progression	NATURE REVIEWS CANCER	2009	1312	93.7
61[82]	Non-muscle myosin II takes centre stage in cell adhesion and migration	NATURE REVIEWS MOL CELL BIOL	2009	1298	92.7
62[83]	Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells	MOLECULAR BIOLOGY OF THE CELL	2001	1298	59.0

63[84]	Autophagosome formation from membrane compartments enriched in phosphatidylinositol 3-phosphate and dynamically connected to the endoplasmic reticulum	JOURNAL OF CELL BIOLOGY	2008	1293	86.2
64[85]	The miR-200 family inhibits epithelial-mesenchymal transition and cancer cell migration by direct targeting of E-cadherin transcriptional repressors ZEB1 and ZEB2	JOURNAL OF BIOLOGICAL CHEMISTRY	2008	1286	85.7
65[86]	Myotubes differentiate optimally on substrates with tissue-like stiffness: pathological implications for soft or stiff microenvironments	JOURNAL OF CELL BIOLOGY	2004	1273	67.0
66[87]	ER Tubules Mark Sites of Mitochondrial Division	SCIENCE	2011	1264	105.3
67[88]	Insight into tubulin regulation from a complex with colchicine and a stathmin-like domain	NATURE	2004	1264	66.5
68[89]	X-ray structure of a CIC	NATURE	2002	1264	60.2
Rank	Article Title	Journal	Publication Year	Times Cited WoS Core	Average per year
	chloride channel at 3.0angstrom reveals the molecular basis of anion selectivity				
69[90]	Lipid rafts: Elusive or illusive?	CELL	2003	1262	63.1
70[91]	Astrocytes, from brain glue to communication elements: The revolution continues	NATURE REVIEWS NEUROSCIENCE	2005	1256	69.8
71[92]	Biology of oligodendrocyte and myelin in the mammalian central nervous system	PHYSIOLOGICAL REVIEWS	2001	1250	56.8
72[93]	Experience-dependent structural synaptic plasticity in the mammalian brain	NATURE REVIEWS NEUROSCIENCE	2009	1247	89.1
73[94]	Openings between defective endothelial cells explain tumor vessel leakiness	AMERICAN JOURNAL OF PATHOLOGY	2000	1239	53.9
74[95]	Nanotubular highways for intercellular organelle transport	SCIENCE	2004	1225	64.5
75[96]	Stress, depression, and neuroplasticity: A convergence of mechanisms	NEUROPSYCHOPHARMACOLOGY	2008	1213	80.9
76[97]	Mesenchymal progenitor cells in human umbilical cord blood	BRITISH JOURNAL OF HAEMATOLOGY	2000	1184	51.5
77[98]	During autophagy mitochondria elongate, are spared from degradation and sustain cell viability	NATURE CELL BIOLOGY	2011	1177	98.1
78[99]	Filopodia: molecular	NATURE	2008	1170	78.0
Rank	Article Title	Journal	Publication Year	Times Cited WoS Core	Average per year
	architecture and cellular functions	REVIEWS MOLECULARCELL BIOLOGY			
79[100]	Microglia in neurodegenerative disease	NATURE REVIEWS NEUROLOGY	2010	1160	89.2
80[101]	Stress, memory and the amygdala	NATURE REVIEWS NEUROSCIENCE	2009	1145	81.8
81[102]	Deconstructing the third dimension - how 3D culture microenvironments alter cellular cues	JOURNAL OF CELL SCIENCE	2012	1144	104.0

82[103]	Phenotypic heterogeneity of the endothelium I. Structure, function, and mechanisms	CIRCULATION RESEARCH	2007	1142	71.4
83[104]	Cellular mechanotransduction: putting all the pieces together again	FASEB JOURNAL	2006	1136	66.8
84[105]	Regulation of actin dynamics through phosphorylation of cofilin by LIM-kinase	NATURE	1998	1136	45.4
85[106]	Structure of the TRPV1 ion channel determined by electron cryo-microscopy	NATURE	2013	1130	113.0
86[107]	Compensation mechanism in tumor cell migration: mesenchymal-amoeboid transition after blocking of pericellular proteolysis	JOURNAL OF CELL BIOLOGY	2003	1115	55.8
87[108]	Focal contacts as	JOURNAL OF	2001	1108	50.4

Rank	Article Title	Journal	Publication Year	Times Cited WoS Core	Average per year
	mechanosensors: Externally applied local mechanical force induces growth of focal contacts by an mDia1-dependent and ROCK-independent mechanism	CELL BIOLOGY			
88[109]	Second-harmonic imaging microscopy for visualizing biomolecular arrays in cells, tissues and organisms	NATURE BIOTECHNOLOGY	2003	1089	54.5
89[110]	Membrane recognition by phospholipid-binding domains	NATURE REVIEWS MOL CELL BIOL	2008	1078	71.9
90[111]	The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses	CELL	2004	1066	56.1
91[112]	Pyramidal neurons: dendritic structure and synaptic integration	NATURE REVIEWS NEUROSCIENCE	2008	1043	69.5
92[113]	Optical deformability as an inherent cell marker for testing malignant transformation and metastatic competence	BIOPHYSICAL JOURNAL	2005	1040	57.8
93[114]	The crystal structure of a voltage-gated sodium channel	NATURE	2011	1034	86.2
94[115]	International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium	PHARMACOLOGICAL REVIEWS	2005	1028	57.1

Rank	Article Title	Journal	Publication Year	Times Cited WoS Core	Average per year
	channels				
95[116]	Structure and gating mechanism of the acetylcholine receptor pore	NATURE	2003	1023	51.2
96[117]	Structure and signalling in the IL-17 receptor family	NATURE REVIEWS IMMUNOLOGY	2009	1019	72.8
97[118]	The biology of YAP/TAZ: hippo signaling and beyond	PHYSIOLOGICAL REVIEWS	2014	1017	113.0
98[119]	A Mechanical Checkpoint Controls Multicellular Growth through YAP/TAZ Regulation by Actin-Processing Factors	CELL	2013	1014	101.4
99[120]	Lipid domain structure of the plasma membrane revealed by patching of membrane components	JOURNAL OF CELL BIOLOGY	1998	1013	40.5
100[22]	Nanoscale architecture of integrin-based cell adhesions	NATURE	2010	1009	77.6

The total citation count for the top 100 articles reached 191,485, with citation densities shown in Table 1. The top 100 articles were published in 43 journals, predominantly in the first quartile (Q1) by category. Eight journals with impact factors exceeding 50 were: Nature (64.8), Science (56.9), Nature Reviews Mol Cell Biol (112.7), Cell (64.5), Nature Reviews Cancer (78.5), Nature Medicine (82.9), Cancer Cell (50.3), and Nature Reviews Immunology (100.3). These eight journals collectively contributed 49 articles, representing 49 % of the top 100 (Table S1 (refer to the online appendix)). Nature Reviews Mol Cell Biol, with the highest impact factor of 112.7, contributed eight articles to the list (17, 52, 55, 56, 58, 65, 82, 99). According to Bradford's Law analysis, the core sources include Nature and Science. As shown in Fig. 1A, Nature published the largest number of papers (16), followed by Science with 12 publications. The top 10 sources together contributed a total of 62 papers in this field (fig. 1, B). Nature not only leads in the number of papers but also ranks first with an H-index of 16 (fig. 1, C). In terms of citations, Journal of Biological Chemistry ranks first with 556 citations, making it the most highly cited journal (fig. 1, D). The substantial contributions from Nature, Science, Nature Reviews Mol Cell Biol, and Cell underscored the pivotal role of high-impact journals in advancing cytomorphology research, highlighting the importance of cell morphology studies in the scientific community.

For the 100 publications, 62 were original articles and 38 were reviews. The 100 publications including basic medical research and engineering research. Table S2 (refer to the online appendix) categorized these articles into topics in cellular biology, focusing on microenvironment, cell signaling pathways, and stem cell research. Attention was given to cellular components like cytoskeleton, chromatin, and mitochondria. The importance of multidisciplinary approaches and emerging technologies, such as imaging and bioengineering, should also be highlighted to stay relevant and impactful.

Publishing Year and Citations

The pace of scientific development and theoretical advancements is often reflected in the number of papers published annually. Fig. 2, A illustrates the annual count of articles, showing a peak in 2008 with 10 influential publications. Fig. 2, B highlights that these highly cited manuscripts span several decades, while fig. 2, C visualizes the relationship between the year of publication and key citation metrics: total citations, average citations per paper, and the number of articles. The highest total citations occurred in 2006 (26,424 citations), while 2017 had the lowest (1,949 citations). The highest average citation per article was observed in 2007 (2,997.8 citations), with the lowest in 2013 (1,072 citations). Table S3 (refer to the online appendix) demonstrated that cell morphology research was most prolific between 1998 and 2012, with notable peaks in the periods 1998–2002 and 2003–2007, based on the number of articles and citation metrics.

Countries or Regions, Institutions, and Authors

A total of 443 authors contributed to the top 100 most-cited papers in cell morphology. The most prolific author was CHEN CS, with four publications, followed by CATTERALL WA, DISCHER DE, DUPONT S, GEIGER B, LANDER ES, MACKINNON R, and PICCOLD S, each contributing three publications (fig. 3, A). In terms of local citations, DISCHER DE led with 22 citations, followed by GEIGER B with 17 citations (fig. 3, B). The consistent productivity of authors such as CHEN CS, CATTERALL WA, GEIGER B, and LANDER ES over more than eight years is illustrated in fig. 3, C. CHEN CS also ranked highest in terms of H-index with a score of 4 (fig. 3, D).

Single-country publications (SCP) are most prominent in the USA, indicating its strong independent research capacity (fig. 4, A). However, multiple-country publications (MCP) were notable in countries like Germany, Italy, Switzerland, and the UK, demonstrating strong international collaborations that contribute to advancing the field of cell morphology. Fig. 5, A shows that the USA was the most cited country with 130,540 citations, followed by the UK (1,745 citations) and Germany (1,380 citations). In terms of publication count, the USA led with 195 papers, followed by Germany (21 papers), Italy (14 papers), and the UK (12 papers) (fig. 5, C). International collaboration was analyzed based on country and institution affiliations. The three-field map (fig. S2, A (refer to the online appendix)) revealed that most authors and affiliations were related to USA, with many authors affiliated with Harvard University.

Fig. S2, B illustrates the bibliographic coupling between countries involved in the top 100 most-cited papers in cell morphology. The United States ranks first with 70 publications, followed by Germany [121] and the United Kingdom [1]. The analysis revealed that the United States is the leading contributor, significantly surpassing other countries in terms of both the number of publications and their impact. This dominance is reflected in extensive research output and collaborations with institutions worldwide. Other notable contributors include the United Kingdom, Germany, and Japan, which also demonstrate substantial contributions and strong international research collaborations. The most prolific institutions include the Harvard University, University of California, and the University of Pennsylvania, all of which have significantly contributed to high-impact research (fig. S2, C).

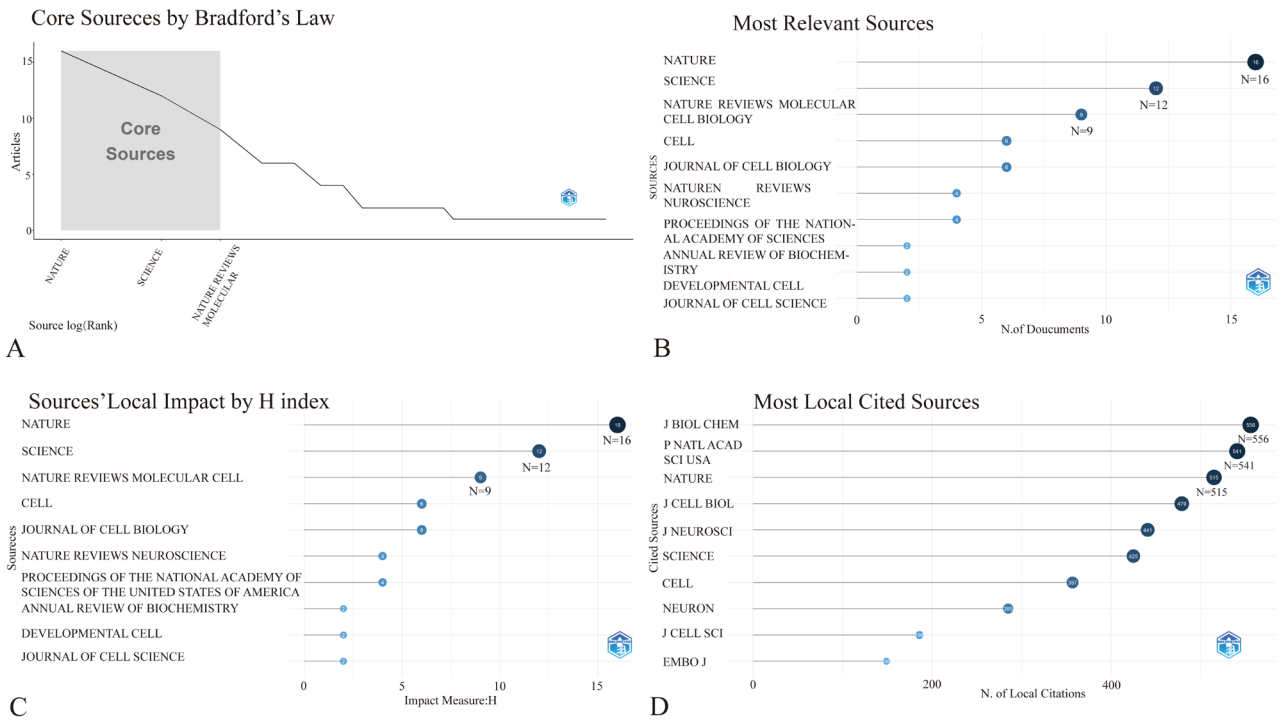

Fig. 1. (A) The top 10 Core journals by Bradford's Law. (B) The number of publications in the top 10 journals. (C) The sources' local impact analysis and visualization among the top 10 journals by H index. (D) The most cited sources analysis in the top 10 journals

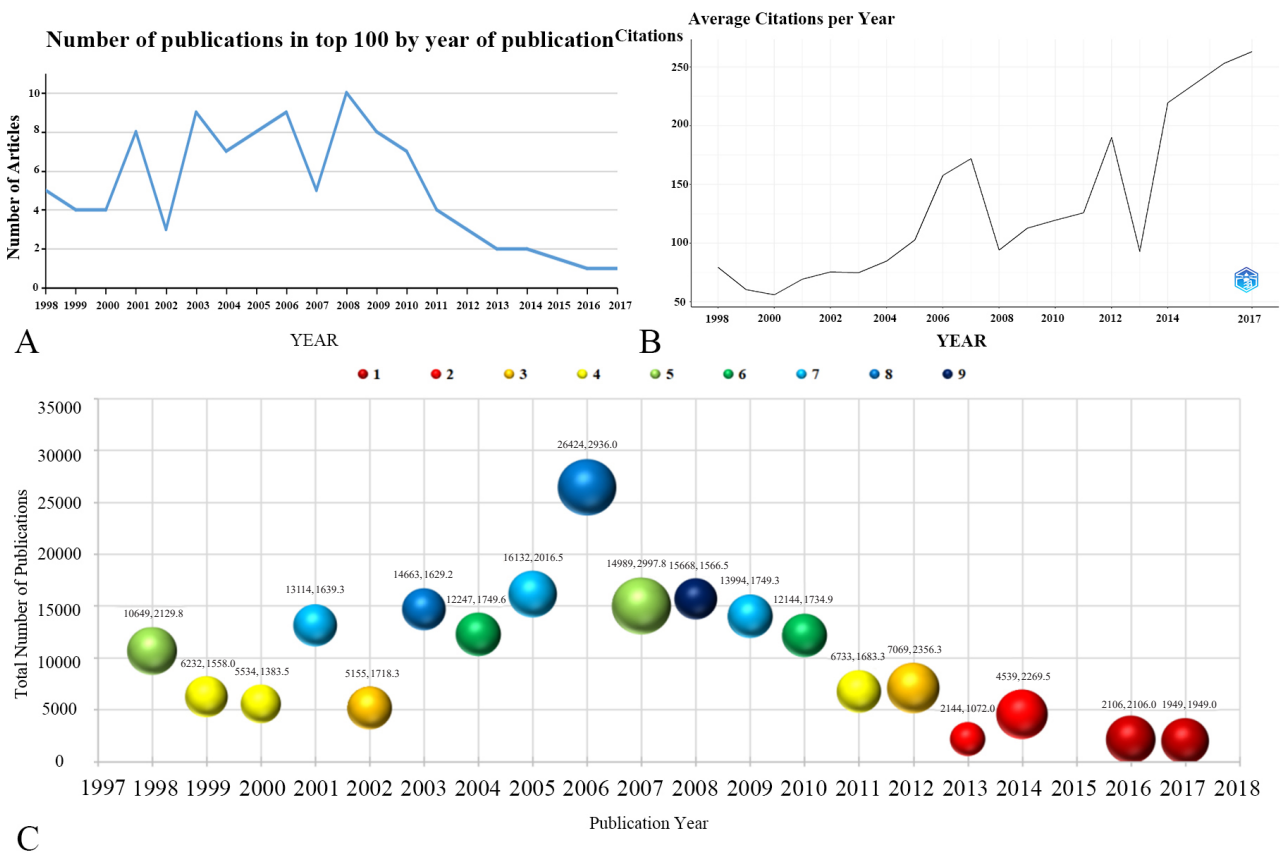

Fig. 2. (A) Line chart of the top 100 publications by year of publication. (B) The average citation trend per year in the top 100 publications. (C) Bubble chart of the year of publication and the top 100 cited articles

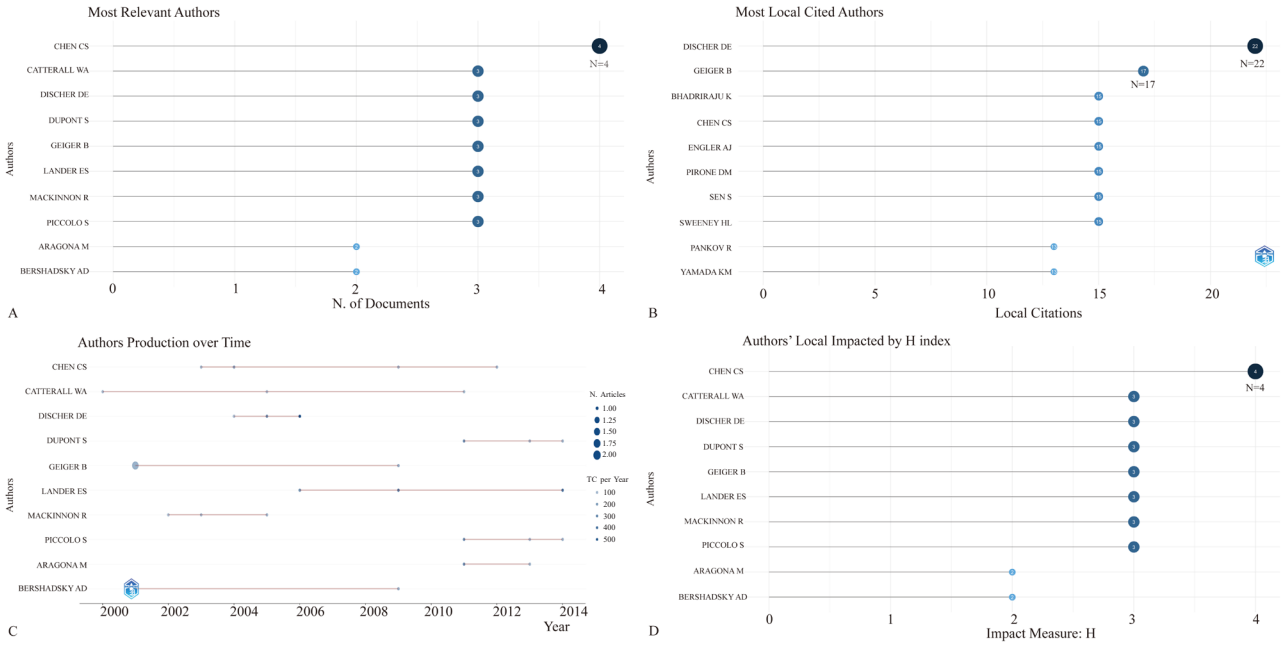

Fig. 3. (A) The top 10 authors on cell morphology in the top 100 publications. (B) The rank of the top 10 authors based on the most local citations in the top 100 publications. (C) The publication trend of the top 10 authors from 2000 to 2014. (D) The top 10 authors based on the local impact by H index

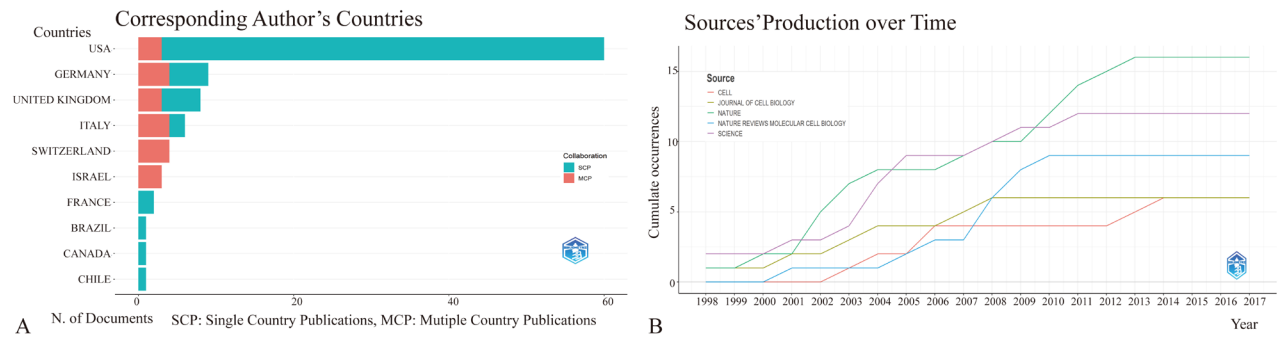

Fig. 4. (A) The top 10 countries visualization studying cell morphology. (B) The sources' production in the top 5 journals from 1998 to 2017

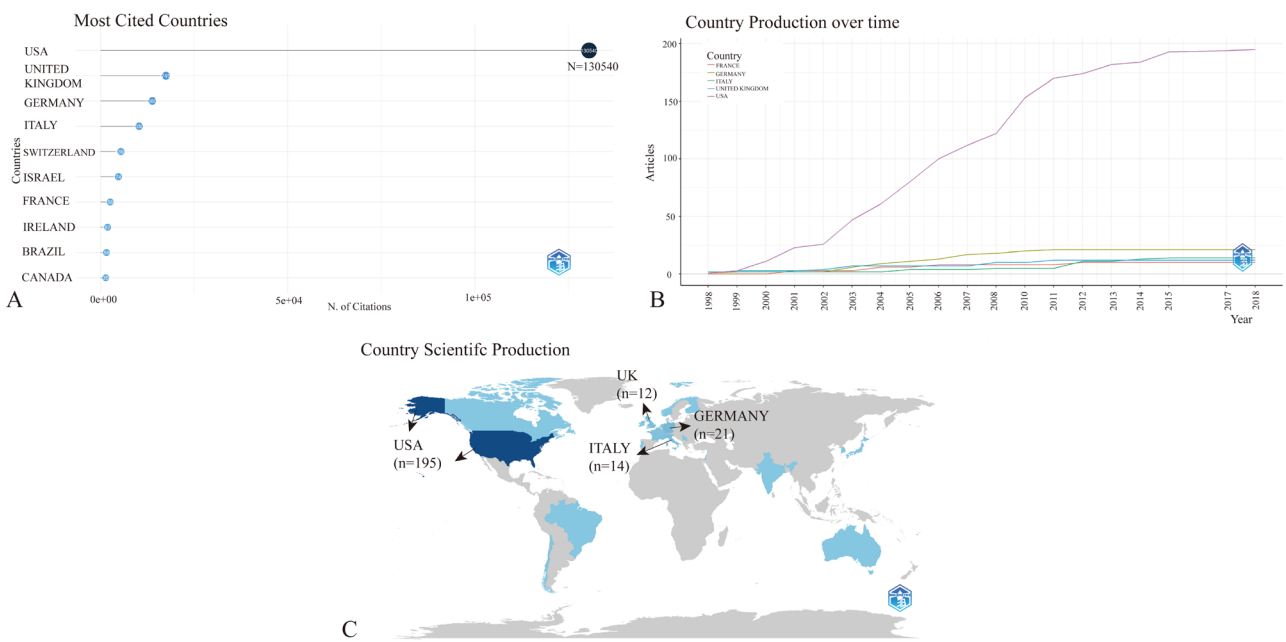

Fig. 5. (A) The citation and visualization analysis among top 10 countries with the publications on cell morphology in the top 100 publications. (B) The publications trend in the field of cell morphology among the top 5 countries from 1998 to 2018. (C) Geographic distribution of global publications on cell morphology in the top 100 publications

Fig. S2, D demonstrates the co-authorship network among the top-cited articles, indicating a high level of collaboration among leading researchers and institutions. Authors were divided into 12 clusters, primarily clustered by Discher, D.E., and Dupont, S. Discher, D.E.'s main contributions are in the mechanical interactions between cells and cellular microenvironment, primarily conducting research in the United States with collaborators mostly from the same country. Dupont, S. focuses on YAP/TAZ signaling and mechanosensing mechanisms, with a geographically diverse set of collaborators and varied research topics. Both Discher, D.E. and Dupont, S. have made substantial contributions to the field, as evidenced by their frequent authorship and co-authorship in high-impact publications.

References Analysis and Keywords

Fig. S3, A (refer to the online appendix) highlights the most locally cited references in cellular morphometry. Studies like Balaban (2001) and Chrzaonowskawodnicka (1996) stand out as the most frequently cited, showcasing their foundational impact on subsequent research. Fig. S3, B (refer to the online appendix) depicts a significant rise in reference citations between 1984 and 2002, reflecting a period of rapid growth and scholarly interest in the field. Fig. S4A and fig. S4, B (refer to the online appendix) present a visual analysis of the most frequently occurring keywords in the top 100 most-cited articles. Terms like "extracellular matrix" and "focal adhesions" are prominently displayed, indicating a concentrated focus on cell structure and adhesion mechanisms. Keywords such as "in vitro" and "in vivo" highlight the balance between experimental models and real biological environments. Other key terms, including "stem cells," "long-term potentiation," "expression," and "differentiation," underscore critical aspects of cellular function and development. Additionally, terms like "endoplasmic reticulum," "actin stress fibers," and "fibroblasts" illustrate the diverse cellular components and mechanisms being studied in this domain.

Discussion

In this study, we employed bibliometric methods to analyze the 100 most cited articles in cell morphology, covering publications from the inception of the field up to April 16, 2023. These articles primarily investigated molecular networks and cellular behaviors associated with cell morphology, including topics such as migration, adhesion, apoptosis, differentiation, cytoskeletal rearrangement, gene/protein regulation, and microenvironmental influences. Prior to 1997, the annual publication counts in cell morphology were relatively low. However, starting from 1998, there was a noticeable increase in the number of related papers, with a peak observed around 2017. The bibliometric analysis further highlighted the sustained interest of the research community in cell morphology. The top 10 articles with the highest citation counts have collectively garnered over 3200 citations, underscoring the field's significance. Given their impact, it was crucial to continue focusing on in-depth research across various domains within cell morphology.

The recognition of aberrant cell shapes as disease markers dates back to the late 19th century, sparking the early development of cytomorphology [122]. By the mid-20th century, techniques such as fine-needle aspiration began using cell and nuclear morphology as diagnostic tools for cancer detection, marking a significant milestone in clinical applications [123]. Entering the 21st century, research in cell morphology has progressed rapidly, revealing deeper connections between cell shape and behaviors such as differentiation, adhesion, and apoptosis. These discoveries have expanded our understanding of how cellular structure influences biological function. Building on these foundations, fig. S5 (refer to the online appendix) presented an updated framework that integrated the essential aspects of cell morphology. It highlighted the role of key cellular components, such as the cytoskeleton and extracellular matrix, in maintaining cell structure and driving functional outcomes. The framework also mapped the current applications of cell morphology, particularly in disease diagnosis, drug development, and regenerative medicine. Additionally, the framework pointed to future directions for the field, emphasizing its intersection with areas like cancer research, neuroscience, and bioinformatics. While these findings aligned with established knowledge in cytomorphology, our study offered a more detailed, structured visualization of how cell morphology contributed to broader biological processes. The comprehensive nature of fig. S5 not only underscored the importance of morphology in cellular biology but also served as a roadmap for future interdisciplinary research. By focusing on real-time morphological changes and their computational modeling, future studies could further explore how these dynamics impacted cellular behavior in different contexts, such as tissue regeneration and cancer metastasis. This approach could lead to the development of novel therapeutic strategies and diagnostic tools based on cellular morphology.

The most cited article, titled 'Matrix Elasticity Directs Stem Cell Lineage Specification,' published in 2006, received 9832 citations. This article provided valuable insights into the contractility and sensitivity of stem cells to the mechanical microenvironment, emphasizing the crucial role

of matrix elasticity in directing stem cell lineage specification and behavior through well-controlled signals. Meanwhile, studies including article [27] discovered that observing cell morphology revealed how cells reacted to varying extracellular matrix stiffness [5, 121]. These studies illustrated how microenvironmental cues closely connect with cell shapes. Surgeons could leverage these insights into the mechanical properties of tissues and cells to improve organ transplantation and stem cell therapy, where the mechanical microenvironment plays a crucial role in patient recovery and tissue integration. The second most cited article provided a comprehensive overview of apoptosis, covering its morphology, biochemistry, role in health and disease, detection methods, and potential alternative forms. In addition, as shown in tab.1, the articles [43, 55, 79] and [98] studied programmed cell death (PCD). As a foundation for studying PCD, morphological analysis remains crucial in understanding the various types of cell death processes, wherein specific vesicles activated by intracellular and extracellular stimuli contributed to the rupture of the cell membrane, subsequently leading to the release of cellular contents [124]. Observation and analysis of cell morphology offered indirect but crucial understanding of the phenotypic characteristics of organisms, providing important reference information for phenotypic research.

The actin cytoskeleton played an important role in the alterations of cell morphology. Ranked third among the top 100 most cited articles, the 1998 publication titled “Rho GTPases and the Actin Cytoskeleton” recorded a total of 5101 citations. This study aimed to elucidate the molecular basis of the actin cytoskeleton, which is crucial for various biological functions in eukaryotic cells. Members of the Rho family of small guanosine triphosphatases (GTPases) were identified as key regulators of the actin cytoskeleton, as evidenced by the findings in articles [33] and [76]. Furthermore, their interactions with multiple target proteins facilitated the coordinated control of diverse cellular activities, including gene transcription and adhesion. Concomitant changes in the actin and microtubule cytoskeletons, microtubule dynamics, and cell morphology were observed to be interconnected [125]. Notably, Rho GTPases and the rearrangement of the actin cytoskeleton were intimately linked to cell morphology studies. Mechanistically, Rho GTPases functioned as molecular switches, relaying signals from cell surface receptors to intracellular effectors, ultimately leading to alterations in cellular behavior and morphology[126]. Recent investigations, including articles [32], [118], and [119] validated the positive role of Rho in YAP/TAZ activation and dephosphorylation, revealing that Rho GTPases could modulate YAP/TAZ activity [118]. These discoveries suggested that there were still critical components of the YAP/TAZ pathway that impact cell morphology and remained to be explored.

The topic of automated cell image analysis gained significant attention due to advancements in image processing technology and algorithms. The open-source CellProfiler project, published in 2006 [34], described a powerful and flexible platform for high-throughput cell image analysis. Prior to this, ImageJ/NIH Image was the only open-source option [127]. Article [51] reviewed the most effective applications of deep learning techniques for developing a classification system to analyze medical images. Microscopy had long been a primary method for studying cellular shapes, but there was a bottleneck at the image analysis stage [128]. Automated image cytometry was preferred over manual analysis as it offered consistent, quantitative measures for each cell, capturing heterogeneity in individual responses, and simultaneously assessing cell shape, size, protein localization, and texture [129]. Multiparametric single-cell data obtained from various types of instruments proved to be more effective than whole-population data (such as western blots or mRNA expression chips) for tasks like clustering genes [130], deriving causal networks [131], classifying protein localization [132], and diagnosing disease [133]. Individual cell measurements could uncover differences in samples that might be masked in whole-population measures. Researchers utilized custom programs written in commercial software (such as MetaMorph, ImagePro Plus, MATLAB) or Java to identify, measure, and track cells in images and time-lapse movies [134]. The increasing availability of single-cell data continued to drive future research in evaluating information content in a data-driven manner. The advanced imaging technologies allowed for detailed cellular and subcellular visualization, which was critical during intraoperative decision-making. Pathologists were able to utilize real-time imaging to guide surgeons in removing cancerous tissues more precisely, ensuring a more effective and targeted approach.

In this analysis, the 100 most-cited articles were published in 43 journals, with impact factors ranging from 1.5 to 112.7. Of these journals, 93.02 % were categorized in the Q1 and Q2 quartiles. Only three journals were from the Q3 and Q4 categories: Journal of Cell Science, Molecular Biology of The Cell, and Toxicologic Pathology. Forty-nine percent of the most-cited articles were published in eight journals with impact factors exceeding 50. Nature Reviews Mol Cell Biol had the highest impact factor of 112.7. The substantial contributions from Nature, Science, Nature Reviews Mol Cell Biol, and Cell underscored the pivotal role of high-impact journals in advancing cytomorphology research and high-

lighted the importance of cell morphology studies in the scientific community. Researchers exhibited a preference for submitting high-quality articles to journals with high impact factors. Consequently, articles published in these journals tended to receive a greater number of citations. Authors of the top 100 most-cited articles were from 17 different countries. Researchers from around the world, particularly in North America and Europe, were heavily involved in studying cell morphology changes and development. Scholars from the University of California, Harvard University, and the University of Pennsylvania showed significant interest in cell morphological studies. Professor Dennis E. Discher from the University of Pennsylvania published the most articles and gained the highest number of citations (3 publications, 16,060 total citations). Discher's work highlighted the complex interplay between cell shape and the extracellular matrix. Authoritative scholarships and key institutions contributing to cell morphology research were elucidated. These findings provided new readers with an accessible overview of cell shapes, their natural history, and trends within the field of cell morphology.

This research revealed a prominent interest in exploring the interplay between microenvironment cues and cell morphology. The pivotal role of microenvironment-related factors in shaping cell morphology likely stemmed from intricate heterogeneity. The microenvironment comprised a vast array of components forming a complex, three-dimensional supramolecular framework. The body's ability to generate a nearly inexhaustible array of microenvironment cues, derived from post-transcriptional splicing of matrix protein-encoding mRNAs and extensive post-translational modifications, enhanced this complexity [135]. The microenvironment was dynamic, responding to perturbations while also remodeling and renewing itself. These dynamic changes significantly influenced cell shapes during all developmental stages [136]. Furthermore, the potential of automated image analysis for increasing the availability of single-cell data drove future research. With advancements in imaging analysis and microscope imaging techniques, the molecular mechanisms of the microstructure were poised to become a key research focus.

Undoubtedly, there were some limitations to our analysis. First, as publications were filtered according to citation numbers, recently published articles with significant impact in the field might have been overlooked and excluded due to their relatively low citation counts. Second, the analysis included various types of papers, such as reviews and articles, which might have introduced omission bias. Third, we only included publications in English recorded on the Web of Science, potentially omitting significant works in other languages or databases.

Conclusion

Cell morphology plays a crucial role in understanding cellular function, disease progression, and tissue development, making it a significant and rapidly evolving research field. This bibliometric analysis highlights key research areas in cell morphology, particularly the mechanical microenvironment, stem cell behavior, and advanced imaging technologies. While these fields are established, our study offers new perspectives on global collaboration trends and the integration of bioinformatics with real-time morphological data, which have the potential to transform surgical decision-making. Future research should focus on applying these advancements to develop predictive models that enhance personalized surgical interventions, bridging the gap between fundamental cellular research and practical clinical applications in areas such as cancer surgery and tissue engineering. This study provides a reference and a new perspective for future research in cell morphology.

Conflict of interest

The authors declare no conflict of interest.

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Compliance with patient rights and principles of bioethics

This study is based on publicly available bibliometric data and does not involve human participants, personal data, or any activity requiring ethical approval.

Authors' contributions

The authors confirm that their contributions meet the authorship criteria established by the ICMJE.

Lin Y.: Study conception and design, data analysis and interpretation, manuscript drafting, development of the research methodology, critical revision of the work, and final approval of the manuscript for publication. Lin Y.:

Zhang Ch.: Study conception and design, data analysis and interpretation, literature review, development of the research methodology, scientific editing, and final approval of the manuscript for publication.

Li Y., Wu H., Li Sh., Cai J., Wang J.: Study conception and design, data analysis and interpretation, literature review, development of the research methodology, technical editing, statistical analysis, and scientific editing.

Kalacheva E.A., Filin A.A., Ch Ding, Shkap M.O.: Data analysis and interpretation, technical editing, reference management, and scientific editing.

Musaev E.R., Ivanov S.A., Zhavoronkov L.P.: Study conception and design, literature review, development of the research methodology, and final approval of the manuscript for publication.

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