Research Article

Regenerative Medicine

Mapping theme trends and knowledge structure on adipose-derived stem cells: a bibliometric analysis from 2003 to 2017

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Aim: To investigate the theme trends and knowledge structure of adipose-derived stem cells (ADSCs) related literatures by using bibliometric analysis. **Materials & methods:** Co-word analysis, strategic diagram and social network analysis were employed. **Results:** In line with strategic diagrams, ADSC differentiation and transplantation as main undeveloped themes in 2003–2007 were partially replaced by regeneration medicine and ADSCs for myocardial infarction in 2008 to 2012, and then partially replaced by miRNAs in ADSC genetics and nerve regeneration in 2013 to 2017. Based on social network analysis, regenerative medicine/methods, myocardial infarction/therapy, as well as miRNAs/genetics, and nerve regeneration/physiology were considered the emerging hot spots in 2008 to 2012 and 2013 to 2017. **Conclusion:** The undeveloped themes and emerging hot spots could be considered as new research topics.

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Keywords: adipose-derived stem cells • bibliometric analysis • co-word analysis • social network analysis • strategic diagram

Adipose-derived stem cells (ADSCs) are adult mesenchymal cells that have the capacity to undergo self-renewal and multipotential differentiation. The ADSCs can be differentiated into diverse cell lineages, which include osteoblasts, chondrocytes, adipocytes, neural cells, cardiomyocytes, vascular endothelial cells, hepatocytes and pancreatic cells [1]. Based on its multipotentiality, ADSCs represent an interesting cell source for a wide range of applications that include diabetes mellitus, liver disease, corneal lesions, neoplastic disease, articular and cutaneous lesions, myocardial infarction, skeletal tissue repair, soft tissue regeneration and ischemic injuries [2–8].

In recent years, along with a rapidly growing number of publications, advancements and novel concepts have been made in the cytology, physiology, metabolism, as well as the application of ADSCs. However, a systematic assessment of ADSC-related research has not been conducted to date.

Hence, bibliometric analysis was used in this study to reveal the trends of research in the field of ADSCs. Bibliometrics is a set of special methods that can be conducted for the quantitative analysis and deciphering of hot spots in the literature. Co-word analysis is the most commonly employed method and is capable of estimating the relationship of two professional words in relevant papers. Biclustering analysis is conducted to classify the extracted professional words. Then, the evolutionary trends and the relationship of themes that can be reflected by the distance between the social network nodes are analyzed using strategic diagram and social network analysis (SNA). Using this approach, in addition to influential publications, countries, journals and authors, this study also identifies the characteristics, internal relationship, theme trends and knowledge structure of the published literatures in the

Future Medicine

ADSC field from 2003 to 2017. The basis and guidelines of future ADSC studies from a bibliometrics perspective are provided here for scientific researchers, clinical doctors and medical educators.

Materials & methods

Data collection

Data were retrieved and downloaded from PubMed (US National Center for Biomedical Information, NIH, MD, USA). Medical subjects headings (MeSH) is the National Library of Medicine curated medical vocabulary resource that has been applied to index and catalog articles in PubMed. By searching with the restriction of language as English and literature type as journal article, relevant articles in PubMed were retrieved in this study. It is noteworthy that no species was excluded in the restriction. It will provide more information of ADSCs from all species instead of just human ADSCs. The 'adipose-derived stem cells' OR 'adipose stem cells' OR 'ADSCs' OR 'adipose tissue-derived mesenchymal stem cells' OR 'adipose-derived stromal cells' OR 'adipose-derived stem/stromal cells' OR 'adipose stromal cells' were selected as the search strategy. Aiming to map theme trends and knowledge structure of ADSCs in the recent 15 years, we established three time periods by each 5 year. Hence, the publication scope fell into three periods: 1 January 2003 to 31 December 2007, 1 January 2008 to 31 December 2012 and 1 January 2013 to 31 December 2017. Based on the titles, abstracts and, in some cases, the full text, two investigators independently screened the results of the primary search. Finally, 159, 1211 and 2770 articles were involved in each period, respectively.

Data extraction & bibliographic matrix setup

The bibliographic information was extracted from PubMed by accurately employing Bibliographic Item Co-Occurrence Matrix Builder (BICOMB) to ultimately generate term-source article and co-occurrence matrix, which served as the fundamental data for the following bibliometric analysis [9]. This study applied BICOMB for determining the distribution characteristics of the publication year, countries, journals, authors and major MeSH terms/MeSH subheadings of the involved literature. The number of high-frequency major MeSH terms/MeSH subheadings were determined using a threshold value (T), which was calculated by the Donohue equation based on high-frequency and low-frequency major MeSH terms/MeSH subheadings: $T = (1 + \sqrt{1 + 8i})/2$, where 'i' denotes the number of major MeSH terms/MeSH subheadings appearing only once [10]. According to this equation, the number of high-frequency major MeSH terms/MeSH subheadings was determined, and the term-source article matrix and co-occurrence matrix were constructed using BICOMB.

Biclustering analysis of the high-frequency major MeSH terms/MeSH subheadings

The biclustering analysis of high-frequency major MeSH terms/MeSH subheadings and PubMed unique identifiers of retrieved ADSC-related articles were employed. Biclustering analysis was conducted to classify the major MeSH/subheading words based on the term-source article matrix. The repeated bisection method in gCLUTO software (http://glaros.dtc.umn.edu/gkhome/cluto/gcluto) was employed in clustering mountain visualization and in constructing a visual matrix [11]. For mountain visualization, each peak in the 3D terrain labeled by a number represents the clusters analyzed by biclustering. The location, volume, height and color of each peak location on the plane were employed to interpret the information relating to the clusters and their associations. The peak location on the plane is the most informative attribute in association with other peaks. The relative similarity of a pair of peaks was estimated by the distance between them. The height of each peak represents the internal similarity of the cluster. The volume of a peak portrays the number of major MeSH terms/MeSH subheadings that are involved in the cluster. Finally, the color of each peak shows the internal standard deviation of a cluster's objects. Red denotes low deviation and, in contrast, blue denotes high deviation. For matrix visualization, the row labels represent high-frequency major MeSH terms/MeSH subheadings, and the column labels stand for PubMed unique identifiers of the articles, which are displayed on the left and the top of the matrix, respectively. Biclustering analysis was used to assess the structure of related research foci.

Strategic diagram analysis

Strategic diagram had been suggested to be utilized to interpret internal and external cohesion of a specific research field by J Law [12]. Based on the co-occurrence matrix, we calculated the centrality and density of each theme cluster. According to theme density and centrality, this study built a 2D strategic diagram by plotting themes along two axes [13,14]. The x-axis represents centrality or the external cohesion index, namely the central position of the theme

within the overall network. The *y*-axis represents density or the internal cohesion index, namely the conceptual development of the theme [14–16]. The calculating methods of centrality and density had been interpreted by M Callon in 1991 [16].

Thus, the x- and *y*-axis generated four quadrants. The major MeSH terms/MeSH subheading clusters were then allocated into different quadrants in line with the results of the biclustering analysis. By comparing the three periods from the strategic diagram, we clearly interpreted various cluster patterns. Additionally, GraphPad 5 software was employed to form a strategic diagram.

Social network analysis

The SNA can be used to analyze structural data and enable the interpretation of the knowledge structure [17]. Centrality measurement is a key method utilized for network analysis, with degree, betweenness and closeness centrality the most widely accepted indexes, which allow comparison of node centrality within networks. A node's degree centrality is the number of direct links, it has with other nodes within the network, which to some extent can indicate the importance of the specific node to the network. The influence of a given node in a network is indicated by the betweenness index, which is calculated by the frequency a node lies on the geodesic paths of other network nodes. LC Freeman had interpreted that the higher the betweenness is, the more powerful the node in controlling other nodes. Closeness centrality is defined as the inverse sum of the shortest distances from a specific node to all other nodes in a network, meaning the higher the closeness centrality, the shorter the distance the node is from other nodes in the network [18,19]. However, degree is suit for research which focuses on co-occurrence of nodes, betweenness for the mediating role of nodes in the whole network and closeness for analyzing the independent and efficacy of nodes. Hence, we chose betweenness to scale node size in this study.

The Ucinet 6.0 (Analytic Technologies Co., KY, USA) software was employed to construct the SNA network base on the high-frequency major MeSH terms/MeSH subheadings co-occurrence matrix. To visualize the network structure, the major MeSH terms/MeSH subheadings networks were presented in 2D maps using the software NetDraw 2.084. The nodes represent the major MeSH terms/MeSH subheadings of the network, and the links stand for their co-occurrence frequency. The locations of these major MeSH terms/MeSH subheadings were evaluated by measuring betweenness centrality of each node to gain insights into the structure of the network on ADSCs.

A graphical workflow of bibliometric analysis is provided in Supplementary Figure 1.

Results

Distribution characteristics of related publications

The search strategy retrieved 159, 1211 and 2770 articles from each period (2003 to 2007, 2008 to 2012 and 2013 to 2017), which were then subjected to comparative analysis. The annual number of ADSC-related articles gradually increased from only 5 in 2003 to 704 in 2017 (Figure 1). The top ten productive countries, journals and authors in each period, which are considered as the core distribution changes in the literature in this research area in the past 15 years, are listed in Table 1. Although the USA is the most productive country among all three periods, its percentage of publications progressively declined. However, England's percentage of publication continuously increased. In 2003 to 2007, the top three journals were Biochemical and Biophysical Research Communications, Tissue Engineering and Stem Cells (OH, USA), and these three journals consisted more than 24% of the total number of searched publications in this field. Then, from 2008 to 2012, these were replaced by Tissue Engineering (Part A), Biomaterials and Stem Cells and Development (Table 1). From 2013 to 2017, the top three journals were *PLoS ONE*, *Tissue Engineering (Part A)* and *Plastic and Reconstructive Surgery*. JS Jung has thus far been the greatest contributor to ADSC researches in 2003 to 2007 and MT Longaker in 2008 to 2012, then Y Zhang in 2013 to 2017.

Research hot spots identified based on MeSH term clusters

For the involved literature in each period, the cumulative frequency percentage of the high-frequency major MeSH terms/MeSH subheadings was 49.4585, 49.6248 and 49.9872% of the total (Supplementary Tables 1–3). These major MeSH terms/MeSH subheadings could be considered as the research hot spots on ADSCs in the past 3 to 5 year time periods.

The MeSH terms, retrieved from 2003 to 2007, were analyzed and classified into three clusters using biclustering analysis. Mountain and matrix visualization of these major MeSH terms/MeSH subheadings are presented in

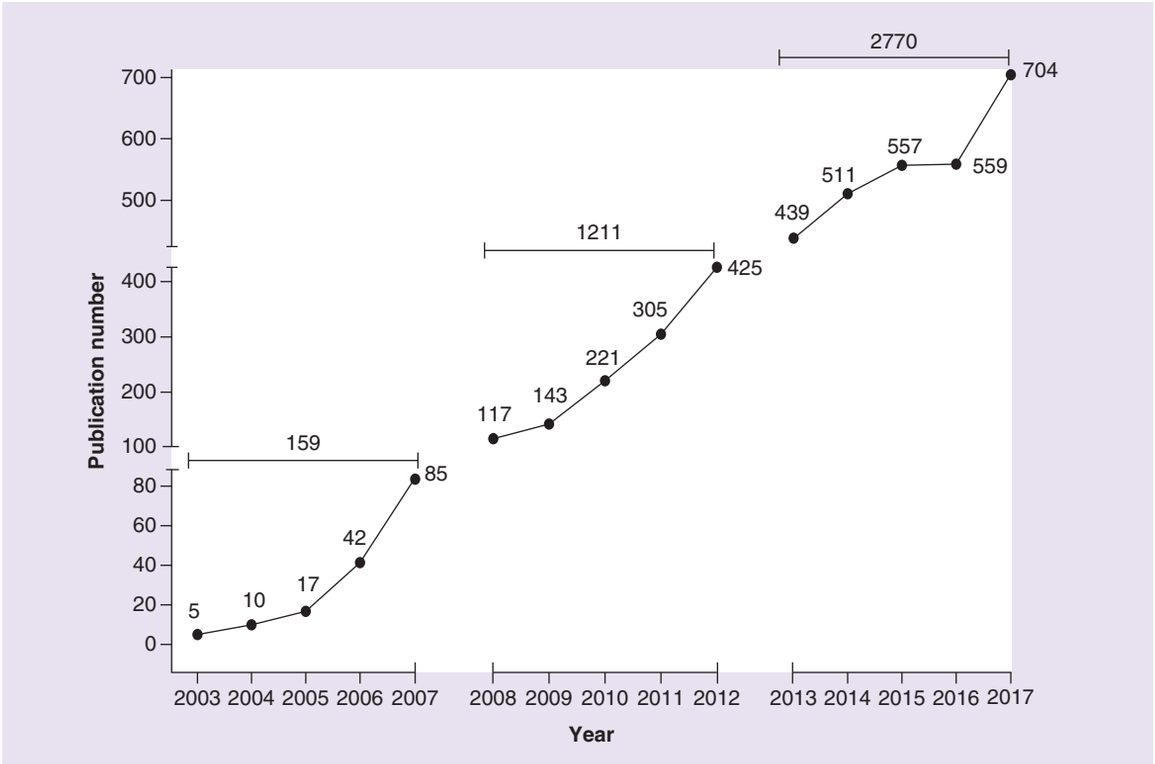

Figure 1. The number of publications on adipose-derived stem cells from 2003 to 2017.

Figure 2. Cluster 1 with red peaks represents the most significant results with low internal standard deviation of a cluster's objects. The results of matrix visualization suggests that 38 high-frequency major MeSH terms/MeSH subheadings (Supplementary Table 1) could be classified into three clusters. The left and top hierarchical trees show the relationships among high-frequency major MeSH terms/MeSH subheadings and that among articles. Additionally, by identifying and summarizing the themes of each cluster, insights into the representative articles of each cluster were attained. The 38 high-frequency major MeSH term/MeSH subheadings are listed on the right side of Figure 2, representing the MeSH terms involved in each cluster. The number before each major MeSH term/MeSH subheading represents its serial number (Supplementary Tables 1–3).

The results of biclustering analysis of major MeSH terms/MeSH subheadings in 2008–2012 and 2013–2017 are shown in Figures 3 and 4 attached, respectively, which is the same as the above. In those two periods, 56 and 81 high-frequency major MeSH terms/MeSH subheadings (Supplementary Tables 2 & 3) are classified into five and six clusters, respectively. The results of cluster analysis of high-frequency major MeSH terms/MeSH subheadings of ADSCs during the three periods are presented in Table 2.

Theme trends of ADSCs

Motor-themes refer to themes located in Quadrant I (upper right), with both strong centrality and high density. In Quadrant II (upper left), those with inadequate external interactions but high density are defined as specialized themes. Themes with weak density and inadequate centrality located in Quadrant III (lower left) are usually considered either emerging or vanishing. Quadrant IV (lower right) contains themes with strong centrality but weak internal maturation [13]. In the strategic diagrams, themes are presented by spheres organized in different quadrants according to their calculated density and centrality, which represent their internal and external cohesion, respectively.

M Callon had interpreted the meaning of strategic diagram in 1991 (Figure 5A). The clusters in Quadrant I are considered central themes in the general network (strongly connected with other clusters) and have intense internal relationships (high degree of development). The clusters located within Quadrant II are considered peripheral but

Table 1. Temporal distribution of publications on adipose-derived stem cells in PubMed (2003–2007, 2008–2012 and 2013–2017).

Period	Rank	Country	Publications, n (%)	Top journal	Publications, n (%)	Author (number of papers)
2003–2007	1	United States	95 (59.7)	*Biochemical and biophysical research communications*	16 (10.1)	JS Jung (18)
	2	Netherlands	26 (16.35)	*Tissue engineering*	13 (8.1)	JH Kim (12)
	3	England	19 (11.9)	*Stem cells (Dayton, OH)*	10 (6.3)	JM Gimble (10)
	4	Switzerland	7 (4.4)	*Biomaterials*	7 (4.4)	YC Bae (10)
	5	China	3 (1.8)	*Plastic and reconstructive surgery*	7 (4.4)	W Tian (8)
	6	Germany	2 (1.2)	*Cells, tissues, organs*	5 (3.1)	W Tang (8)
	7	United Arab Emirates	2 (1.2)	*Molecular and cellular biochemistry*	5 (3.1)	HY Song (8)
	8	India	1 (0.6)	*The international journal of biochemistry & cell biology*	4 (2.5)	ES Jeon (8)
	9	Japan	1 (0.6)	*Annals of plastic surgery*	3 (1.9)	L Liu (8)
	10	Scotland	1 (0.6)	*Cytotherapy*	3 (1.9)	Y Lin (8)
	Total		157 (98.7)		73 (45.9)	
2008–2012	1	United States	635 (52.4)	*Tissue engineering (Part A)*	69 (5.7)	MT Longaker (40)
	2	England	235 (19.4)	*Biomaterials*	49 (4.0)	JH Kim (32)
	3	Netherlands	125 (10.3)	*Stem cells and development*	44 (3.6)	JM Gimble (29)
	4	Germany	44 (3.6)	*Plastic and reconstructive surgery*	42 (3.5)	H Mizuno (25)
	5	Switzerland	24 (1.9)	*Stem cells (Dayton, OH)*	34 (2.8)	JP Rubin (23)
	6	United Arab Emirates	19 (1.6)	*Methods in molecular biology (NJ, USA)*	32 (2.6)	Y Zhang (20)
	7	Korea (South)	19 (1.6)	*Journal of tissue engineering and regenerative medicine*	30 (2.5)	AW James (19)
	8	Japan	16 (1.3)	*Cell transplantation*	22 (1.8)	KG Marra (19)
	9	India	13 (1.1)	*Tissue engineering (Part C), methods*	19 (1.6)	B Levi (19)
	10	China	11 (0.9)	*Journal of biomedical materials research (Part A)*	17 (1.4)	SH Lee (18)
	Total		1151 (94.2)		358 (29.3)	
2013–2017	1	United States	1320 (47.0)	*PLoS ONE*	115 (4.1)	Y Zhang (62)
	2	England	667 (24.1)	*Tissue engineering (Part A)*	81 (2.9)	Y Wang (60)
	3	Netherlands	225 (8.1)	*Plastic and reconstructive surgery*	72 (2.6)	Y Liu (48)
	4	Switzerland	89 (3.2)	*Journal of tissue engineering and regenerative medicine*	63 (2.3)	X Wang (46)
	5	Germany	86 (3.1)	*Biomaterials*	61 (2.2)	P Zhang (38)
	6	Greece	52 (1.9)	*Stem cell research and therapy*	56 (2.0)	J Wang (34)
	7	Korea (South)	47 (1.7)	*Scientific reports*	52 (1.9)	X Zhang (33)
	8	Iran	41 (1.5)	*Stem cells international*	51 (1.8)	RL Reis (30)
	9	Japan	26 (0.9)	*Stem cells translational medicine*	49 (1.8)	MT Longaker (30)
	10	India	25 (0.9)	*Stem cells and development*	44 (1.6)	L Wang (30)
	Total		2560 (92.4)		644 (23.2)	

already well-developed themes. The clusters in Quadrant III are both peripheral and undeveloped. The clusters in Quadrant IV are central and undeveloped, yet they are becoming mature to some extent [16].

The area of the spheres is proportional to the number of high-frequency major MeSH terms/MeSH subheadings involved in each theme cluster (Figure 5B–D). From 2003 to 2007, Cluster 1, which is in Quadrant I and stands for the researches on adipose tissues and stem cell cytology and physiology, cell differentiation physiology and cell culture techniques were developed and in the core status with adequate centrality and high density. Clusters 0 and 2 in Quadrant III represent the researches on ADSC physiology and transplantation and ischemia therapy, as well

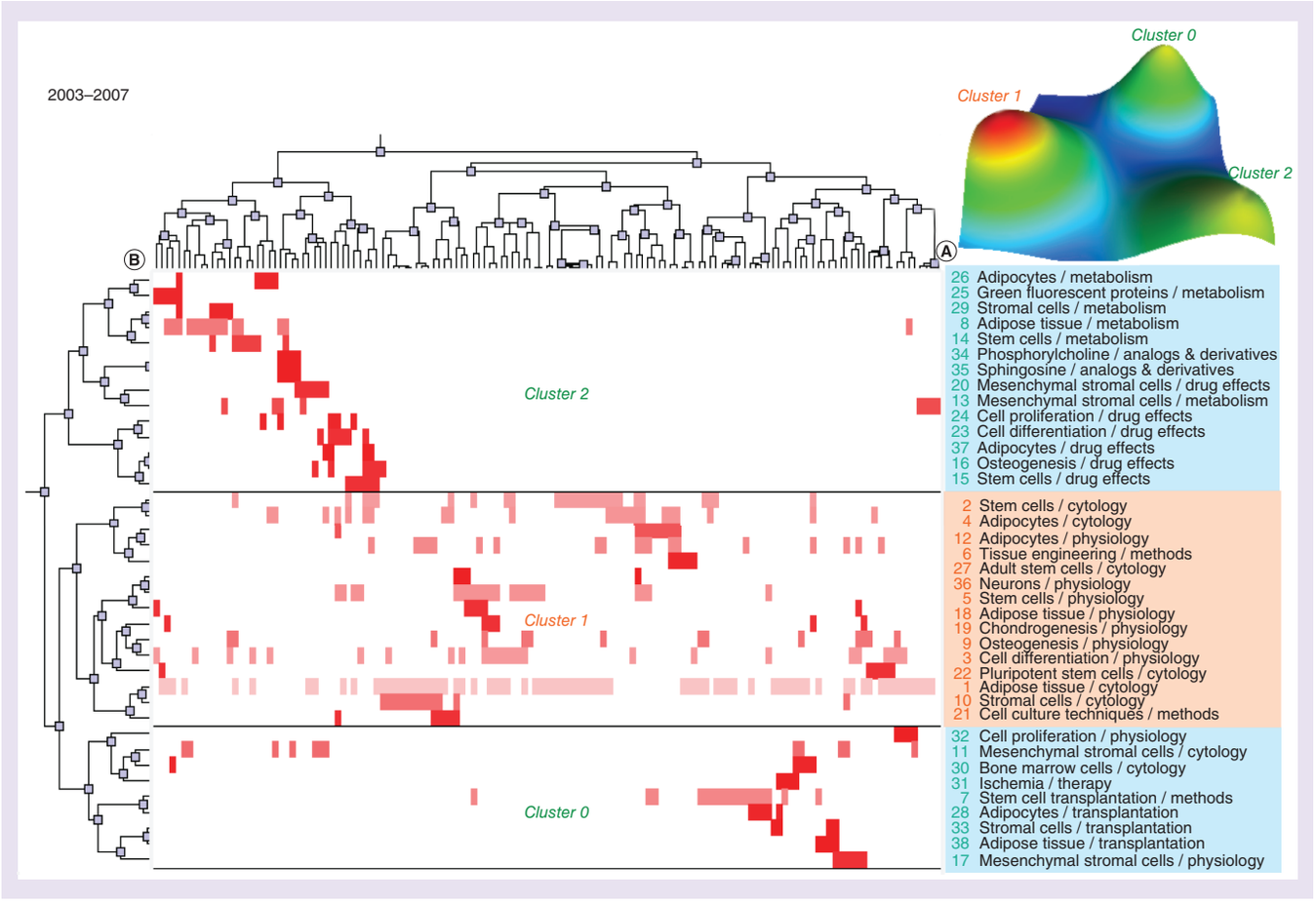

Figure 2. Biclustering analysis of 38 high-frequency major medical subjects heading terms/medical subjects heading subheadings and articles on adipose-derived stem cells in 2003 to 2007. (A) Mountain visualization of biclustering of 38 high-frequency major MeSH terms/MeSH subheadings and articles. **(B)** Matrix visualization of biclustering of 38 high-frequency major MeSH terms/MeSH subheadings and PubMed unique identifier of articles. The number before each major MeSH terms/MeSH subheading represents the serial number as shown in Supplementary Table 1.
MeSH: Medical subjects heading.

as metabolism, and ADSC proliferation and differentiation induced by drugs were not mature, in other words, on the edge of the research in the field of ADSCs.

Some immature clusters in Quadrant III in 2003–2007, such as ADSCs, osteogenic and chondrogenic differentiation exhibited sustained development and were considered as developed themes in 2008–2012. Meanwhile, biocompatible materials and tissue engineering were newly developed themes. Furthermore, the main undeveloped themes were partially replaced by ADSC differentiation genetics and pharmacology, neovascularization, regeneration medicine and wound healing, and myocardial infarction therapy.

By comparing the data from 2008 to 2012, ADSC neuron differentiation, conditioned culture media and bone regeneration physiology were located within Quadrant I, representing newly developed themes in the recent 5 years (2013–2017). In the meantime, adult stem cell transplantation and physiology, ADSCs for nerve regeneration and reconstructive surgical procedures, as well as ADSC neovascularization and wound-healing pharmacology and signal transduction, which were situated within Quadrant III, were considered as new main undeveloped themes in addition to the two remaining undeveloped themes in 2008–2012.

Those three strategic diagrams indicated the tendency and development of each theme cluster of ADSCs during three different periods.

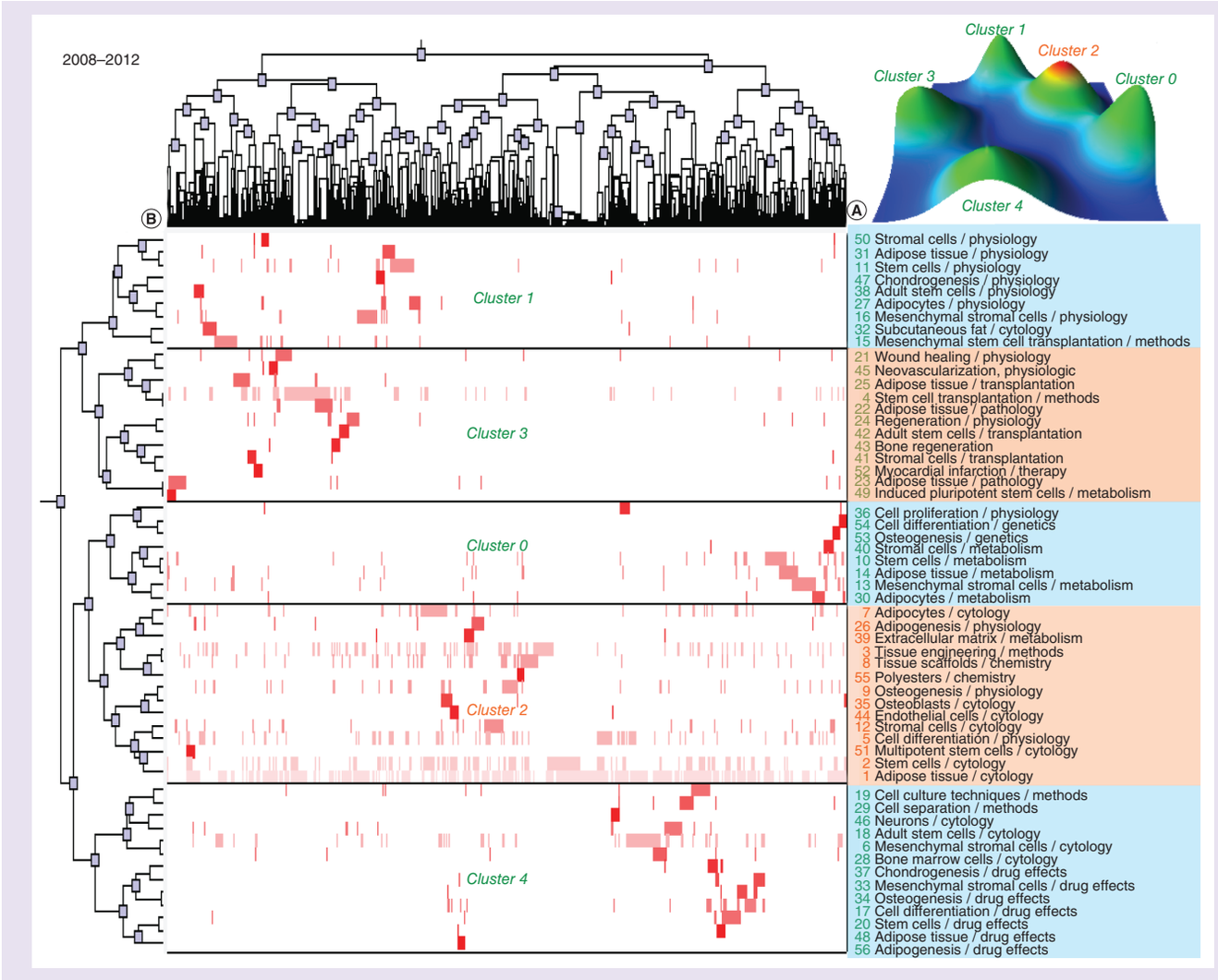

Figure 3. Biclustering analysis of 56 high-frequency major medical subjects heading terms/medical subjects heading subheadings and articles on adipose-derived stem cell in 2008–2012. (A) Mountain visualization of biclustering of 56 high-frequency major MeSH terms/MeSH subheadings and articles. **(B)** Matrix visualization of biclustering of 56 high-frequency major MeSH terms/MeSH subheadings and PubMed unique identifier of articles. The number before each major MeSH terms/MeSH subheading represents the serial number as shown in Supplementary Table 2.
MeSH: Medical subjects heading.

Knowledge structure of ADSCs

Three SNAs are presented in Figure 6, and centrality parameters such as degree, betweenness and closeness (Supplementary Tables 4–6) were employed to analyze the knowledge structure of the SNA networks. To better understand the results, all of the SNAs were drawn based on betweenness centrality. The size of the nodes is proportional to the major MeSH terms/MeSH subheadings betweenness centrality, and the thickness of lines stands for the co-occurrence frequency (Figure 6).

In the network of ADSCs during 2003–2007, nine major MeSH terms/MeSH subheadings (blue and yellow circles in Figure 6A) are shown to have high degree of centrality (>28), and the top nine high-frequency major MeSH terms/MeSH subheadings are also involved. Among these nine high-frequency major MeSH term/MeSH subheadings, adipose tissue/cytology showed the highest degree of centrality (150; Supplementary Table 4). The top two betweenness centrality values listed in the Supplementary Table 4 are 144.221 and 52.64, representing adipose tissue/cytology and cell differentiation/physiology, respectively. These two major MeSH terms/MeSH

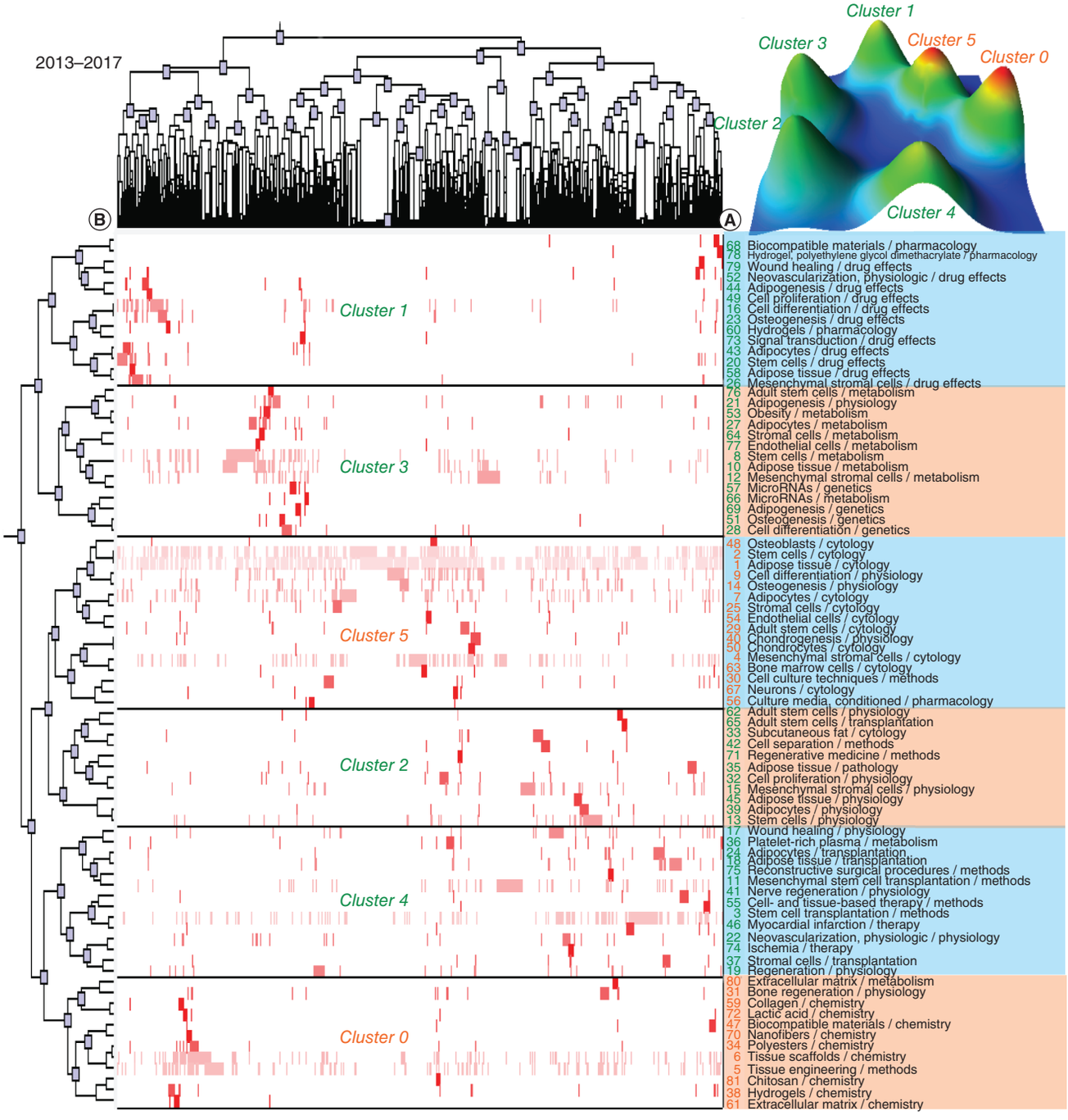

Figure 4. Biclustering analysis of 81 high-frequency major major medical subjects heading terms/major medical subjects heading subheadings and articles on adipose-derived stem cells in 2013–2017. (A) Mountain visualization of biclustering of 81 high-frequency major MeSH terms/MeSH subheadings and articles. **(B)** Matrix visualization of biclustering of 81 high-frequency major MeSH terms/MeSH subheadings and PubMed unique identifier of articles. The number before each major MeSH terms/MeSH subheading represents the serial number as shown in Supplementary Table 3.
MeSH: Medical subjects heading.

Table 2. Cluster analysis of high-frequency major medical subjects heading terms/medical subjects heading subheadings of adipose-derived stem cells in 2003–2007, 2008–2012 and 2013–2017.

Period	Cluster	Number of MeSH terms[†]	Cluster analysis
2003–2007	0	32,11,30,31,7,28,33,38,17	1. ADSC physiology and transplantation; 2. ADSCs for ischemia therapy
	1	2,4,12,6,27,36,5,18,19,9,3,22,1,10,21	1. Adipose tissue and stem cells cytology and physiology; 2. Cell differentiation physiology and cell culture techniques
	2	26,25,29,8,14,34,35,20,13,24,23,37,16,15	1. ADSC metabolism; 2. ADSC proliferation and differentiation induced by drug
2008–2012	0	36,54,53,40,10,14,13,30	1. ADSC metabolism; 2. ADSC cell differentiation genetics
	1	50,31,11,47,38,27,16,32,15	1. ADSC cytology and chondrogenesis physiology
	2	7,26,39,3,8,55,9,35,44,12,5,51,2,1	1. Biocompatible material and tissue engineering; 2. ADSC osteogenesis physiology; 3. Extracellular matrix metabolism
	3	21,45,25,4,22,24,42,43,41,52,23,49	1. ADSC transplantation and neovascularization; 2. Regenerative medicine and wound healing; 3. ADSCs for myocardial infarction therapy
	4	19,29,46,18,6,28,37,33,34,17,20,48,56	1. ADSC differentiation induced by drug
2013–2017	0	80,31,59,72,47,70,34,6,5,81,38,61	1. Bone regeneration physiology; 2. Biocompatible materials and tissue engineering; 3. Extracellular matrix metabolism
	1	68,78,79,52,44,49,16,23,60,73,43,20,58,26	1. ADSC proliferation, differentiation, neovascularization and wound-healing pharmacology; 2. ADSC signal transduction
	2	62,65,33,42,71,35,32,15,45,39,13	1. Regenerative medicine; 2. Adult stem cells transplantation and physiology
	3	76,21,53,27,64,77,8,10,12,57,66,69,51,28	1. ADSC metabolism and differentiation genetics; 2. miRNAs in ADSC genetics
	4	17,36,24,18,75,11,41,55,3,46,22,74,37,19	1. Wound-healing physiology; 2. ADSCs for myocardial infarction, nerve regeneration, ishemia and reconstructive surgical procedures; 3. ADSC neovacularization physiology
	5	48,2,1,9,14,7,25,54,29,40,50,4,63,30,67,56	1. ADSC physiology and cytology; 2. ADSC osteogenesis, chondrogenesis and neuron differentiation; 3. ADSC conditioned culture media

[†]Represents the serial number of high-frequency major MeSH terms/MeSH subheadings in each period which shown in Supplementary Tables 1–3.
ADSC: Adipose-derived stem cell; MeSH: Medical subjects heading.

subheadings play the strongest mediating role in the network. Both terms have highest closeness values of 34 and 30, respectively, suggesting that they have a tight connection with the other nodes.

Besides the two major MeSH terms/MeSH subheadings with high betweenness values earlier mentioned, other major MeSH terms/MeSH subheadings such as stem cell/cytology, adipocytes/cytology, stem cells/physiology, tissue engineering/methods, stem cell transplantation/methods, adipose tissue/metabolism, as well as osteogenesis/physiology also have high betweenness centrality. This suggests that these also play a critical mediating role in the network. The mean betweenness centrality was 13.526 ± 25.071 (Supplementary Table 7).

Four new major MeSH terms/MeSH subheadings (magenta circle in Figure 6B), tissue scaffolds/chemistry, stem cell/metabolism, mesenchymal stromal cells/cytology and stromal cell/cytology were added to the nodes with high individual centrality in 2008–2012 by comparing with the SNA of 2003–2007. However, adipose tissue/cytology still showed the highest degree and betweenness centrality values (Supplementary Table 5).

Total of 11 new emerging nodes (magenta box in Figure 6B) located at the edge of the network, such as regeneration/physiology, neovascularization/physiology, wound healing/physiology and myocardial infarction/therapy and bone regeneration, were considered as emerging hot spots of ADSC research in 2008–2012 (Figure 6B).

In the SNA of 2013–2017, five new major MeSH terms/MeSH subheadings (green circle in Figure 6C), in other words, cell differentiation/drug effects, wound healing/physiology, mesenchymal stromal cells/metabolism, mesenchymal stem cell transplantation/methods and mesenchymal stromal cells/physiology were added to

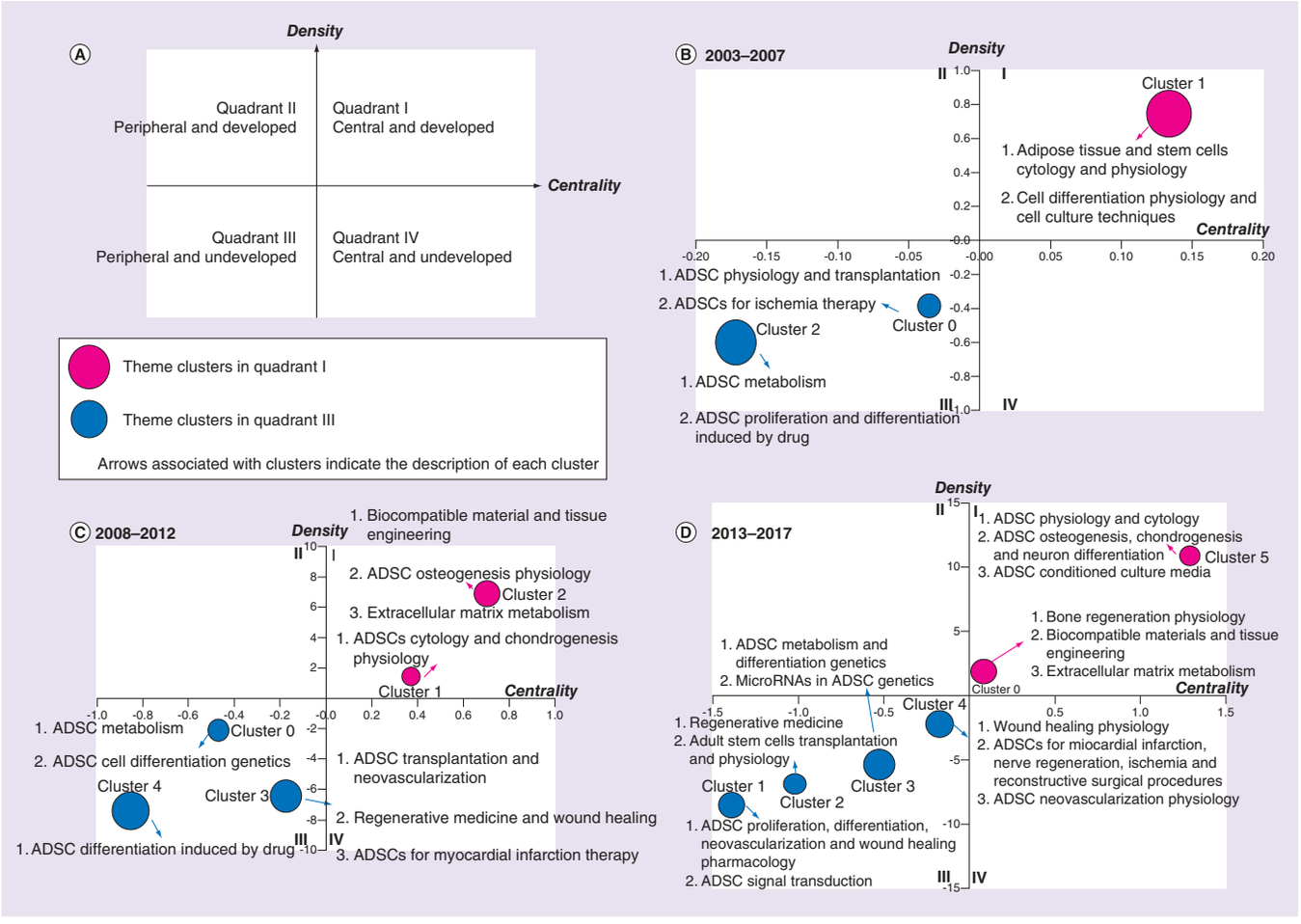

Figure 5. Strategic diagrams for adipose-derived stem cells. (A) The meaning of strategic diagram. **(B)** Strategic diagram for ADSCs in 2003–2007. **(C)** Strategic diagram for ADSCs in 2008–2012. **(D)** Strategic diagram for ADSCs in 2013–2017. Clusters in each strategic diagram refer to the biclustering results presented in Table 2. The size of a signal node represents the number of major MeSH terms/MeSH subheadings involved in each cluster. Arrows associated with clusters indicate the description of each cluster.
ADSC: Adipose-derived stem cell; MeSH: Medical subjects heading.

the nodes characterized by high betweenness. Total of 12 new emerging nodes in Figure 6C (green box), such as osteogenesis/genetics, neovascularization/drug effects, mesenchymal stromal cells/drug effects, wound healing/drug effect, miRNAs/genetics, miRNAs/metabolism, nerve regeneration/physiology and reconstructive surgical procedure/methods, were considered as emerging hot spots of ADSC research in 2013–2017. Three individual centrality values in 2008–2012 are listed in Supplementary Table 6. Also, the individual centrality and network centralization of the entire three periods are listed in Supplementary Table 7.

Discussion

The number of studies on ADSCs has soared with increasing awareness of its potential clinical applications. The ADSCs have become an emerging research field, which requires the systematic analysis of theme trends and knowledge structure. The co-word analysis, biclustering analysis, strategic diagram and SNA were integrated in this study to investigate knowledge structure and its evolution in the past 15 years.

In this study, we report for the first time an evaluation of ADSC-related research around the world in recent decades: there has been rapid growth in ADSC-related publications in the last 15 years (2003–2017); the articles published in the last period are two and tenfold higher than the second and first periods, respectively; ADSC physiology, metabolism, proliferation, differentiation and transplantation as major undeveloped themes during the first period were partially replaced by ADSCs and neovascularization, regeneration medicine, and

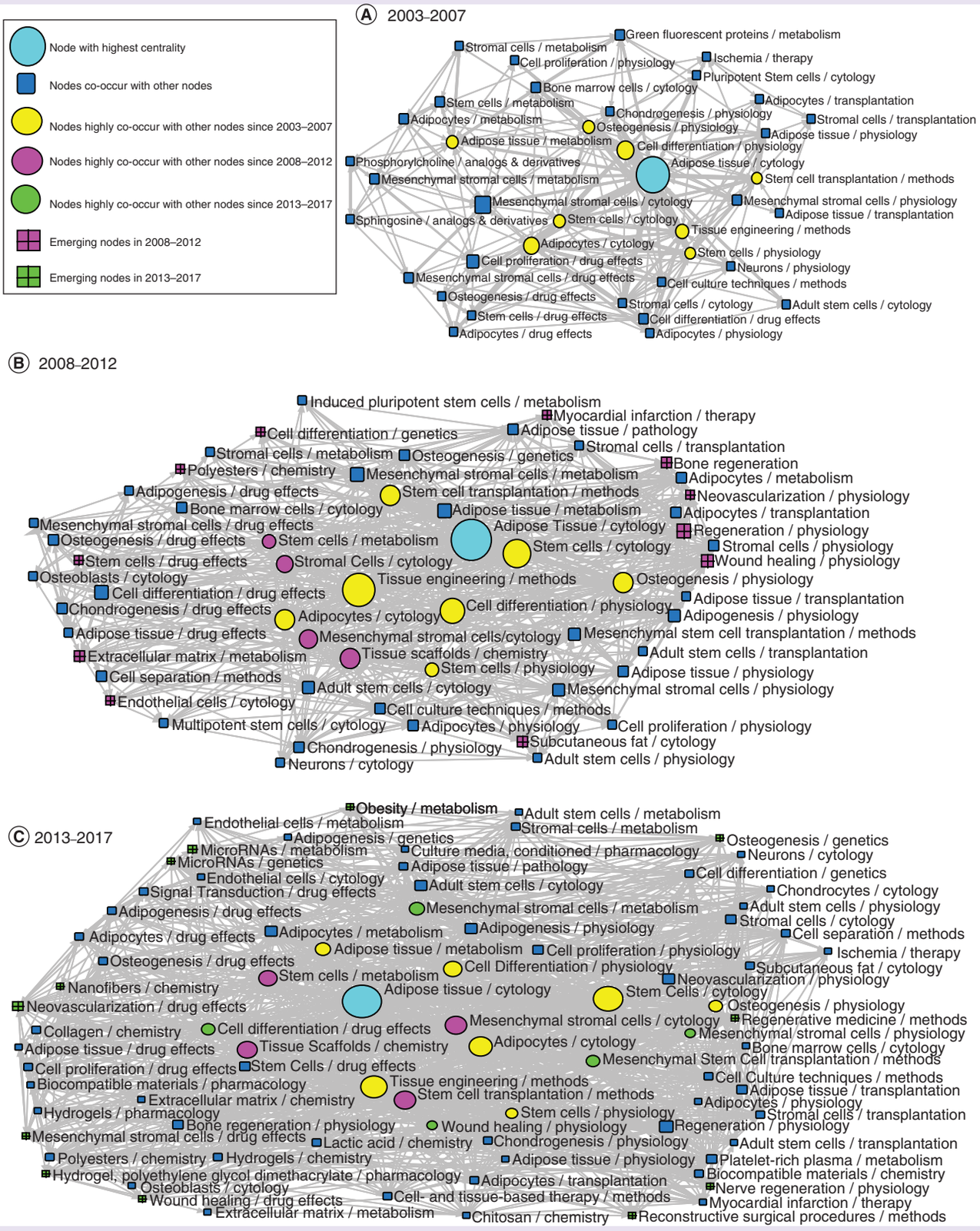

Figure 6. Social network analysis for major medical subjects heading terms/medical subjects heading subheadings in adipose-derived stem cells-related publications. (A) Social network analysis for 38 major MeSH terms/MeSH subheadings in 2003–2007. **(B)** Social network analysis for 56 major MeSH terms/MeSH subheadings in 2008–2012. **(C)** Social network analysis for 81 major MeSH terms/MeSH subheadings in 2013–2017. The size of the nodes indicates MeSH terms centrality. The thickness of the lines indicates the co-occurrence frequency of MeSH terms pairs.
MeSH: Medical subjects heading.

wound healing and ADSCs for myocardial infarction in the second period, then partially replaced by miRNAs in ADSC genetics and ADSCs for nerve regeneration and reconstructive surgical procedures in the third period, as indicated by the strategic diagrams and adipose tissue/cytology, cell differentiation/physiology, stem cells/cytology, stem cell transplantation/methods, adipocytes/cytology, stem cells/physiology, as well as tissue engineering/methods were core topics among three periods based on SNA, yet 11 new emerging nodes, such as regenerative medicine/methods, neovascularization/physiology and wound healing/physiology, myocardial infarction/therapy, and 12 new emerging nodes, such as miRNAs/genetics and nerve regeneration/physiology, and reconstructive surgical procedures/methods, were considered as emerging hot spots during the second and third periods, respectively.

Since Zuk *et al.* had successfully isolated stem cells from human adipose tissues in 2001 [20], more researchers were attracted by its self-renewal and multipotential differentiation. In particular, a considerable amount of ADSC-related publications (2770) emerged in the last 5 years.

A strategic diagram was employed to interpret the theme trends during the three periods. In the first period (2003–2007), only one cluster located within Quadrant I had been well developed. Cluster 1 related to adipose tissue and stem cell cytology and physiology had been established [21–24], and thus used of an ADSC research focus. During that period, the rest of the two clusters were located within Quadrant III. Numerous research focused on ADSC physiology and transplantation [25,26], such as identification and isolation of ADSCs that were immature and need further investigations. In addition, the culture effect of serial factors on multiple differentiation, such as chondrogenesis, osteogenensis, cardiomyocyte and even neuron differentiation of ADSCs, were underdeveloped [27–34]. Meanwhile, ADSCs had been considered applicable for ischemic disease therapy [35].

During the second period (2008–2012), ADSC osteogenic and chondrogenic differentiation (partial themes of clusters 1 and 2), which were considered as undeveloped themes in the first period, had progressed well [36–38] and were then located within Quadrant I. Furthermore, biocompatible material and tissue engineering was a newly developed theme [39]. Cluster 4, which is associated with ADSCs differentiation, including neuron differentiation, remained as an undeveloped theme as their capacity to differentiate into neurons had not been elucidated at that time [40,41]. Furthermore, Cluster 3, which is associated with ADSC neovascularization, regeneration medicine, and wound healing and ADSCs for myocardial infarction therapy were new undeveloped themes compared with the first period. It has been suggested that ADSC transplantation improves neovascularization in diabetic wound healing [42]. Further studies should elucidate the molecular mechanisms underlying the development of potential therapeutic medicine for nervous system diseases, although diverse transcription factors, signaling molecules and key marker genes had been shown to participate in intermediate stages of ADSC neuronal differentiation [43]. Due to its multipotential differentiation capability, ADSCs were initially thought to be as the main regenerative medicine approach [44,45]. Beitnes *et al.* had then reported that intramyocardial injections of human mesenchymal stem cells following acute myocardial infarction improves left ventricular function [46].

The strategic diagram of the third period (2013–2017) represents the knowledge structure in the last 5 years and provides a large amount of information on new projects. Neuron differentiation in ADSCs then emerged as a new well-developed theme that was associated with Cluster 5 in Quadrant I. Different protocols and neural markers employed in each procedure for ADSC neuron differentiation and possible mechanisms have recently been reported [47,48]. In particular, Petersen *et al.* presented a method for directly obtaining neural stem cells from adipose tissues that are capable of differentiating into functional neuronal cells without going through intermediates, such as ADSCs [49]. In terms of various recently emerged undeveloped themes in Quadrant III, those of in cluster 4 were associated with ADSCs for nerve regeneration and reconstructive surgical procedures, cluster 1 was associated with ADSC neovascularization and wound-healing pharmacology and cluster 3 was associated with miRNAs in ADSC genetics, which require further investigations. In recent years, ADSC transplantation has been considered as a highly potential technique for peripheral nerve regeneration, and the progress in reconstructive surgical procedures using ADSCs has been reported in 2012 [50–52].

Although ADSC-related miRNAs, such as miR-17 and miR-31, and their pivotal roles in regulating the proliferation and differentiation of ADSCs have been identified in numerous research, further investigations on their underlying mechanism are warranted [53–55]. Furthermore, ADSCs for myocardial infarction therapy remain an undeveloped theme during this period. Although ADSCs have emerged as a novel treatment for cardiovascular diseases and related investigations have moved into Phase I and II clinical traits, various limitations remain, including low survival and engraftment [56].

In parallel, three SNAs generated by high-frequency MeSH terms shows that the top 9, 12 and 17 major MeSH terms/MeSH subheadings also have comparatively high degree centrality during the three periods, respectively. The SNA becomes more extensive and intensive from the first period to the second, then to the third.

However, based on degree and betweenness centrality, we conclude that major MeSH terms/MeSH subheadings, such as 'adipose tissue/cytology', has the largest number of direct connections with other nodes, facilitates in the development of the field of ADSCs during all three periods and is situated at the core position of the whole network. This suggests that it plays the greatest potential role in mediating the co-occurrence of other nodes. Furthermore, there are 11 and 12 MeSH terms (magenta and green boxes in Figure 6B & C, respectively), which are located at the edge of the network in the second and third periods, respectively. This phenomenon suggests that regenerative medicine/methods, neovascularization/physiology and myocardial infarction/therapy in Figure 6B and miRNAs/genetics and nerve regeneration/physiology and reconstructive surgical procedures/methods in Figure 6C are emerging fields.

This is the first comprehensive study that analyzed and evaluated ADSC-related research using bibliometrics. Here, ADSCs remain in the primary developmental stages and may be potentially employed in future applications. Further research is required to investigate the undeveloped and emerging hot spots mentioned above. Hence, these results will scientifically provide a basis and guidelines for ADSC study for scientific researchers, clinical doctors and medical educators when launching new projects.

Our study has certain limitations. The first involves the inclusion and exclusion criteria of the literature. In this study, we excluded reviews and other types of literature, except for journal articles. If review articles are excluded, then it is possible to miss some research hot spots. Second, co-word analysis is based on high-frequency MeSH terms. Thus, the number of high-frequency MeSH terms might, to some extent, impact the results of clustering analysis, and new emerging topics with low attention may not have been involved. Therefore, diverse databases and analyses should be utilized in future studies.

Conclusion

Based on the co-word analysis of high-frequency MeSH terms on ADSCs, the biclustering analysis, strategic diagram and SNA were integrated in this study. This study suggested that undeveloped themes in recent decades, such as ADSC neovascularization, regeneration medicine and wound healing, ADSCs for myocardial infarction, and miRNAs in ADSC genetics and nerve regeneration could be considered as the most attractive themes. Also, adipose tissue and stem cell cytology, stem cell transplantation, tissue engineering and cell differentiation of ADSCs are core topics that have undergone continuous development from 2003 to 2017. Regenerative medicine, neovascularization, myocardial infarction, miRNAs in ADSC genetics and nerve regeneration were considered as emerging hot spots for ADSCs during recent decades. This presentation of detailed data can help scientific researchers and clinical doctors generally understand the past, present and future of ADSCs.

Summary points

- The bibliometric approach based on co-word analysis, strategic diagram, and social network analysis with publication data allows visualization of the theme trends and knowledge structure of adipose-derived stem cells (ADSCs).
- We identified the development of ADSC research across each 5 year period in terms of publication volume, distribution characteristics (country, journal and author), research themes and hot spots.
- Based on these findings, ADSC neovascularization, regenerative medicine, miRNAs in ADSC genetics, ADSCs for myocardial infarction, nerve regeneration and reconstructive surgical procedures were main undeveloped themes and emerging hot spots in the recent 5 years.
- Bibliometric approaches offer valuable information on research policies and innovation strategies. This study provides a fresh perspective for understanding the past, present and future

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at:

www.futuremedicine.com/doi/suppl/10.2217/rme-2018-0117

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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