OBERSEMINAR 27.11.2019

A bibliometric analysis of IL-35 research from 2009 to 2018

Atheroprotective roles of smooth muscle cell phenotypic modulation

TEXT MINING & SCRNA-SEQ

PeerJ

A bibliometric analysis of IL-35 research from 2009 to 2018

Xulong Cai, Chenrong Zhou, Li Zhou and Qiaolan Xu

Department of Pediatrics, Yancheng Third People's Hospital, Yancheng, Jiangsu, China

ABSTRACT

Background. Interleukin-35 (IL-35) is a recently discovered cytokine that plays a role in immune suppression and has therefore been the subject of a great deal of research. A bibliometric analysis of the global research concerning IL-35, however, is rare.

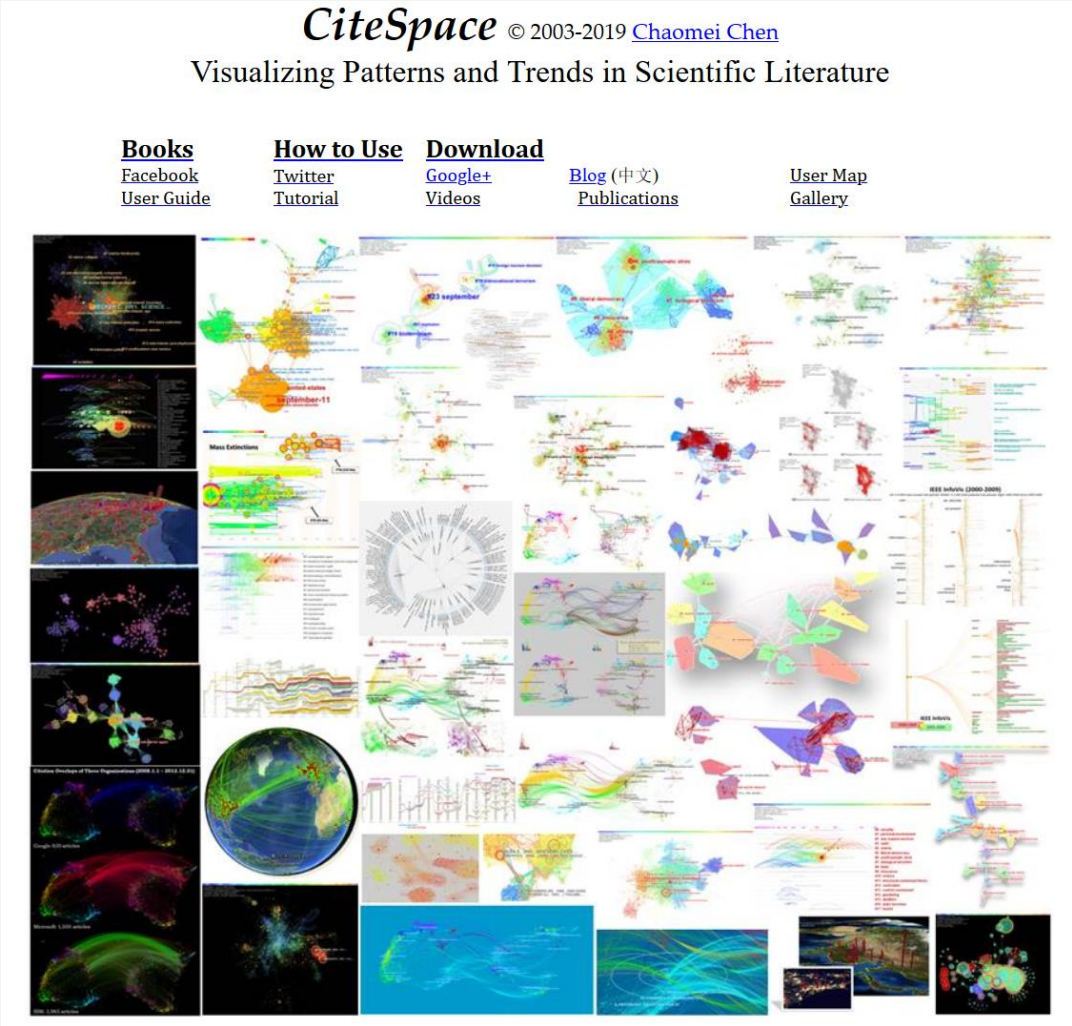
Objectives. The aim of this research was to assess the international scientific output of IL-35 research and explore its hotspots and frontiers from 2009 to 2018 by bibliometric analysis.

Methods. Publications about IL-35 research from 2009 to 2018 were retrieved from the Web of Science Core Collection (WoSCC). Citespace V was used to analyze years, journals, countries, research institutions, areas of exploration, research hotspots, and trends of publication.

Results. We retrieved a total of 416 publications and observed a trend of publications increasing over the past decade. Original articles (351) were the most frequently occurring document type. The largest number of publications belonging to one country and one institution, respectively, was China (202) and Tianjin Medical University (17). Trending keywords may indicate frontier topics, including "infectious tolerance," "autoimmune," and "central nervous system."

Conclusion. This study provides valuable information on the study of IL-35 so that researchers may identify new research fields.

Text → CiteSpace



Journal of the American Society for Information Science and Technology

Volume 57, Issue 3
1 February 2006
Pages 359-377

Research Article

CiteSpace II: Detecting and visualizing emerging trends and transient patterns in scientific literature

Chaomei Chen

First published: 14 December 2005 | https://doi.org/10.1002/asi.20317 | Citations: 786

The concept of an intellectual base is useful to further clarify the nature of a research front (Persson, 1994). If we define a research front as the state of the art of a specialty (i.e., a line of research), what is cited by the research front forms its intellectual base. A specialty can be conceptualized as a time-variant mapping $\Phi(t)$ from its research front $\Psi(t)$ to its intellectual base $\Omega(t)$.

$$\Phi(t) : \Psi(t) \rightarrow \Omega(t)$$

The goal of our research is to develop a generic approach that can be used to detect and visualize emerging trends and abrupt changes in $\Phi(t)$ over time. In particular, $\Psi(t)$ is a group of words and phrases (i.e., *terms*) associated with emerging trends and sudden changes at time t. These terms are called *research-front terms*. $\Omega(t)$ consists of groups of articles cited by articles in which research-front terms were found.

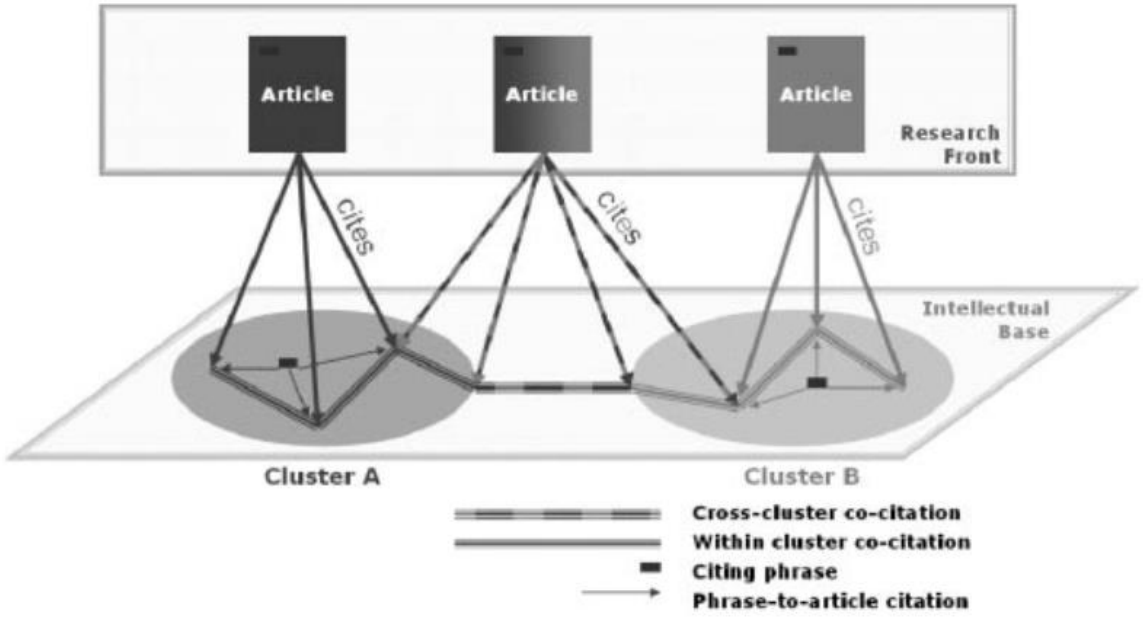


FIG. 1. The conceptual model of CiteSpace II. Time-sliced snapshots are devised to highlight changes of prominent specialties over time.

- IL35 is a member of the IL12 family
  - IL12 family: IL12/23/27
- Increased interest in IL35

- Few attempts, however, have been made to systematically analyse the knowledge, intellectual turning points and key points in this field.

Results structured as follows:

1. General information
2. Journal Analysis
3. Country and institution analysis
4. Research area analysis
5. Co-citation analysis
6. Keyword analysis

General information

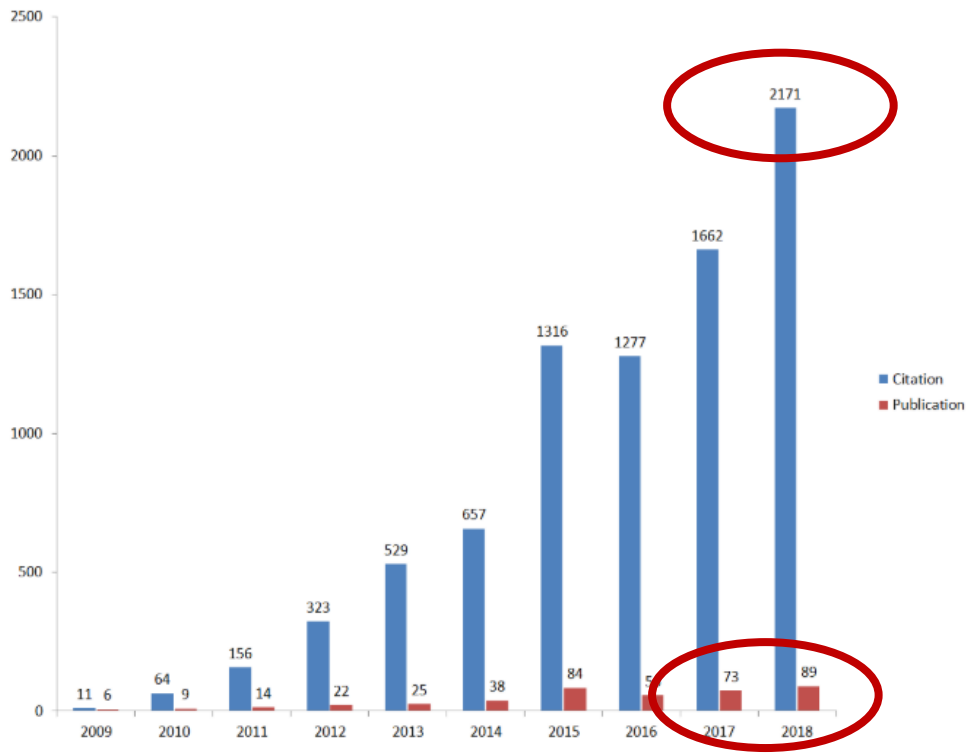


Figure 1 **The number of publications and citations from 2009 to 2018.** (A) The number of research papers published on il-35 was increasing from 2009 to 2018. (B) The frequency of citation of research papers on il-35 had increased significantly in the past decade.

Full-size DOI: 10.7717/peerj.7992/fig-1

Journal Analysis

Table 1 Top 10 most cited articles on IL-35.

Rank	First Author	Year	Title	Journal	Impact Factor (2017)	Cited
1	Lauren W. Collison	2010	IL-35-mediated induction of a potent regulatory T cell population	Nature Immunology	21.8	408
2	Ping Shen	2014	IL-35-producing B cells are critical regulators of immunity during autoimmune and infectious diseases	Nature	41.6	378
3	Ren-Xi Wang	2014	Interleukin-35 induces regulatory B cells that suppress autoimmune disease	Nature Medicine	32.6	254
4	Lauren W. Collison	2012	The composition and signaling of the IL-35 receptor are unconventional	Nature Immunology	21.8	181
5	Lauren W. Collison	2009	Regulatory T Cell Suppression Is Potentiated by Target T Cells in a Cell Contact, IL-35-and IL-10-Dependent Manner	The Journal of Immunology	4.54	150
6	Veronika Bachanova	2014	Clearance of acute myeloid leukemia by haploidentical natural killer cells is improved using IL-2 diphtheria toxin fusion protein	Blood	15.1	149
7	Irina Kochetkova	2010	IL-35 Stimulation of CD39(+) Regulatory T Cells Confers Protection against Collagen II-Induced Arthritis via the Production of IL-10	The Journal of Immunology	4.54	133
8	Xinyuan Li	2012	IL-35 Is a Novel Responsive Anti-inflammatory Cytokine - A New System of Categorizing Anti-inflammatory Cytokines	PLoS One	2.77	110
9	Gregory S. Whitehead	2012	IL-35 production by inducible costimulator (ICOS)-positive regulatory T cells reverses established IL-17-dependent allergic airways disease	Journal of Allergy and Clinical Immunology	13.3	110
10	Stefan Wirtz	2011	Interleukin-35 Mediates Mucosal Immune Responses That Protect Against T-Cell-Dependent Colitis	Gastroenterology	20.8	106

Table 2 The top 5 most productive and cited journals.

Rank	Productive journals	The number of published papers	Rank	Cited journal	Cited frequency
1	Cytokine	19	1	Frontiers in Immunology	223
2	PLoS One	16	2	PLoS One	167
3	The Journal of Immunology	14	3	The Journal of Immunology	136
4	Frontiers in Immunology	10	4	Scientific Reports	82
5	Journal of Interferon and Cytokine Research	8	5	Cytokine	75

Country/Institution analysis

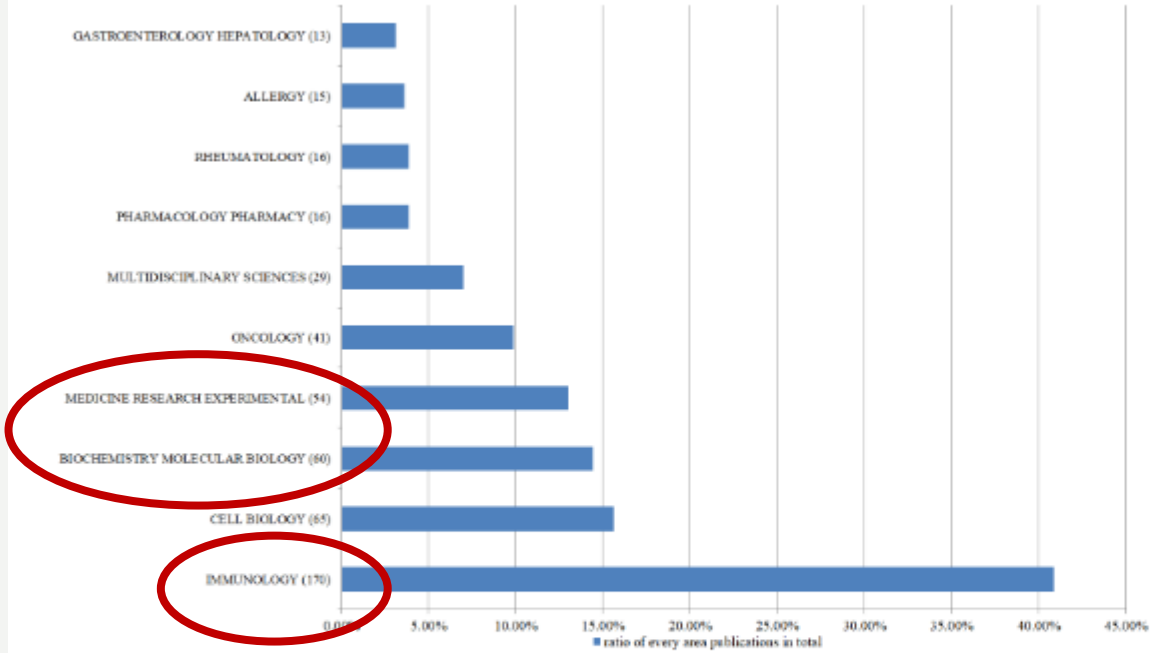
Table 3 Top 10 prolifc countries publishing paper on IL-35.

Rank	Country	Frequency
1	China	202
2	USA	91
3	Germany	26
4	Iran	18
5	Japan	16
6	Italy	11
7	Turkey	10
8	Canada	9
9	England	8
10	France	8

Table 4 Top 10 prolifc institutions publishing paper on IL-35.

Rank	Institution	Frequency
1	TIANJIN MEDICAL UNIVERSITY	17
2	ST JUDE CHILDREN S RESEARCH HOSPITAL	15
3	NATIONAL INSTITUTES OF HEALTH NIH USA PENNSYLVANIA COMMONWEALTH SYSTEM OF HIGHER EDUCATION	14
4	PCSHE	14
5	SHANDONG UNIVERSITY	13
6	ANHUI MEDICAL UNIVERSITY	9
7	CHINA MEDICAL UNIVERSITY	9
8	HUAZHONG UNIVERSITY OF SCIENCE TECHNOLOGY	9
9	JILIN UNIVERSITY	9
10	NIH NATIONAL EYE INSTITUTE NEI	9

Research area analysis



How is a research area defined?

Figure 2 **The top 10 most frequently appearing research areas in IL-35 studies from 2009 to 2018.** In recent 10 years, the research on IL-35 mainly involves immunology.

Full-size DOI: 10.7717/peerj.7992/fig-2

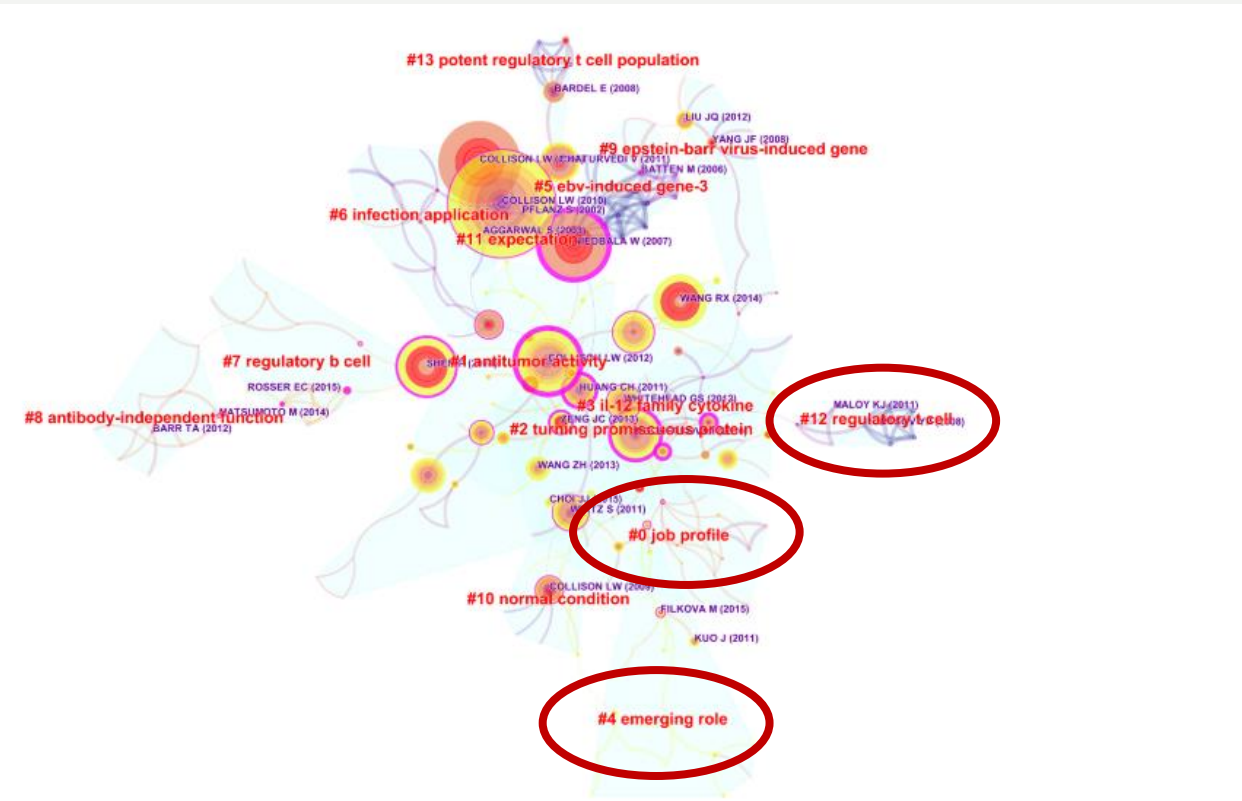


Figure 3 **Reference co-citation map of articles related to IL-35 research published from 2009 to 2018.** (A) Red labels represented different clusters. (B) "#0, #1, #2, #3…" were the serial number of the clusters. (C) The red circle of the node indicated that the citation frequency of the literature increases suddenly in a given period of time.

Full-size DOI: 10.7717/peerj.7992/fig-3

Keyword analysis

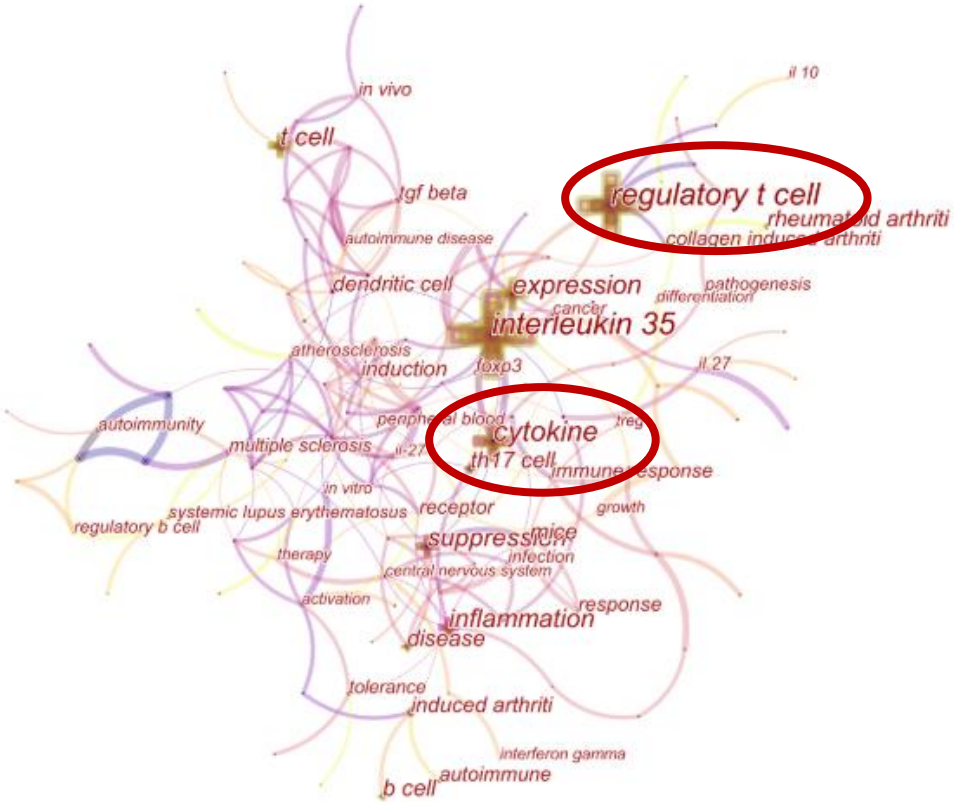


Figure 5 **A keyword co-occurrence map of IL-35 from 2009 to 2018.** The node size represented the co-occurrence frequency of keyword. The larger the node size indicated the higher the keyword frequency.

Full-size DOI: 10.7717/peerj.7992/fig-5

Keyword analysis

Keywords	Year	Strength	Begin	End	2009 - 2018
ror gamma t	2009	2.46	**2009**	2011	
multiple sclerosis	2009	2.438	**2009**	2011	
growth factor beta	2009	2.4413	**2009**	2012	
dendritic cell	2009	3.9714	**2009**	2011	
central nervous system	2009	4.0623	**2010**	2014	
suppression	2009	3.511	**2010**	2013	
il 27	2009	3.5542	**2012**	2013	
ulcerative coliti	2009	2.4646	**2012**	2014	
cutting edge	2009	2.5643	**2012**	2013	
infectious tolerance	2009	2.7033	**2012**	2015	
autoimmunity	2009	2.6384	**2015**	2016	
cell	2009	2.4221	**2016**	2018	

Figure 6 **Top 12 keywords with strongest citation bursts.** Burst strength: the intensity of the sudden increase of keyword citation frequency in a certain period of time. Research frontiers are identified based on burst keywords.

Full-size DOI: 10.7717/peerj.7992/fig-6

Timeline plot of co-citation

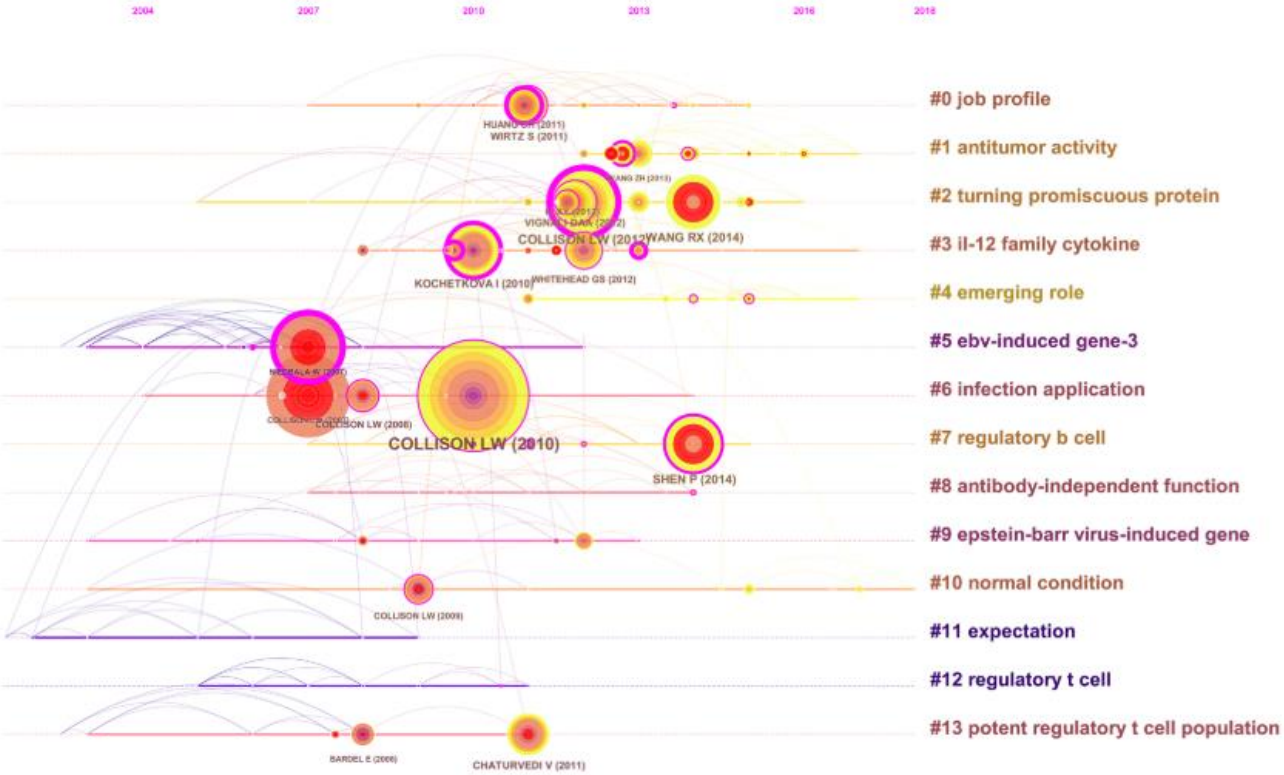


Figure 4 **Reference co-citation time-view map of articles related to IL-35 research published from 2009 to 2018.** (A) From #0 to #13, the clusters size decreased gradually. (B) From left to right, it means the time span from the past to 2018.

Full-size DOI: 10.7717/peerj.7992/fig-4

Conclusion

- Interesting analysis of literature data
- Could serve as a template for reports from an integrated system at our chair
  - Keywords and research areas should be defined

A bibliometric analysis of IL-35 research from 2009 to 2018

Atheroprotective roles of smooth muscle cell phenotypic modulation

TEXT MINING & SCRNA-SEQ

ARTICLES
https://doi.org/10.1038/s41591-019-0512-5
nature medicine

Atheroprotective roles of smooth muscle cell phenotypic modulation and the *TCF21* disease gene as revealed by single-cell analysis

Perlen!

Robert C. Wirka[1,2], Dhananjay Wagh[3], David T. Paik[1,2], Milos Pjanic[1,2], Trieu Nguyen[1,2], Clint L. Miller[4], Ramen Kundu[1,2], Manabu Nagao[1,2], John Coller[3], Tiffany K. Koyano[5], Robyn Fong[5], Y. Joseph Woo[5], Boxiang Liu[6], Stephen B. Montgomery[6], Joseph C. Wu[1,2], Kuixi Zhu[7,8], Rui Chang[7,8], Melissa Alamprese[7,8], Michelle D. Tallquist[9], Juyong B. Kim[1,2,10] and Thomas Quertermous[1,2,10]*

In response to various stimuli, vascular smooth muscle cells (SMCs) can de-differentiate, proliferate and migrate in a process known as phenotypic modulation. However, the phenotype of modulated SMCs in vivo during atherosclerosis and the influence of this process on coronary artery disease (CAD) risk have not been clearly established. Using single-cell RNA sequencing, we comprehensively characterized the transcriptomic phenotype of modulated SMCs in vivo in atherosclerotic lesions of both mouse and human arteries and found that these cells transform into unique fibroblast-like cells, termed 'fibromyocytes', rather than into a classical macrophage phenotype. SMC-specific knockout of *TCF21*—a causal CAD gene—markedly inhibited SMC phenotypic modulation in mice, leading to the presence of fewer fibromyocytes within lesions as well as within the protective fibrous cap of the lesions. Moreover, *TCF21* expression was strongly associated with SMC phenotypic modulation in diseased human coronary arteries, and higher levels of *TCF21* expression were associated with decreased CAD risk in human CAD-relevant tissues. These results establish a protective role for both *TCF21* and SMC phenotypic modulation in this disease.

ARTICLES
https://doi.org/10.1038/s41591-019-0512-5

nature medicine

Atheroprotective roles of smooth muscle cell phenotypic modulation and the *TCF21* disease gene as revealed by single-cell analysis

Robert C. Wirka[1,2], Dhananjay Wagh[3], David T. Paik[1,2], Milos Pjanic[1,2], Trieu Nguyen[1,2], Clint L. Miller[4], Ramen Kundu[1,2], Manabu Nagao[1,2], John Coller[3], Tiffany K. Koyano[5], Robyn Fong[5], Y. Joseph Woo[5], Boxiang Liu[6], Stephen B. Montgomery[6], Joseph C. Wu[1,2], Kuixi Zhu[7,8], Rui Chang[7,8], Melissa Alamprese[7,8], Michelle D. Tallquist[9], Juyong B. Kim[1,2,10] and Thomas Quertermous[1,2,10]*

In response to various stimuli, vascular smooth muscle cells (SMCs) can de-differentiate, proliferate and migrate in a process known as phenotypic modulation. However, the phenotype of modulated SMCs in vivo during atherosclerosis and the influence of this process on coronary artery disease (CAD) risk have not been clearly established. Using single-cell RNA sequencing, we comprehensively characterized the transcriptomic phenotype of modulated SMCs in vivo in atherosclerotic lesions of both mouse and human arteries and found that these cells transform into unique fibroblast-like cells, termed 'fibromyocytes', rather than into a classical macrophage phenotype. SMC-specific knockout of *TCF21*—a causal CAD gene—markedly inhibited SMC phenotypic modulation in mice, leading to the presence of fewer fibromyocytes within lesions as well as within the protective fibrous cap of the lesions. Moreover, *TCF21* expression was strongly associated with SMC phenotypic modulation in diseased human coronary arteries, and higher levels of *TCF21* expression were associated with decreased CAD risk in human CAD-relevant tissues. These results establish a protective role for both *TCF21* and SMC phenotypic modulation in this disease.

scRNA-seq

- SMCs develop into distinct phenotypes
  - Pro-inflammatory, dysfunctional macrophage-like cells: Lgals3 up
  - Synthetic SMCs that may contribute to the protective fibrous cap, which would serve to prevent plaque rupture and myocardial infarction

- Tcf21 expressed in proepicardial cells giving rise to cardiac fibroblasts and coronary artery SMCs

- Labeled Myh11 (SMC origin vs. other cells)

scRNA-seq

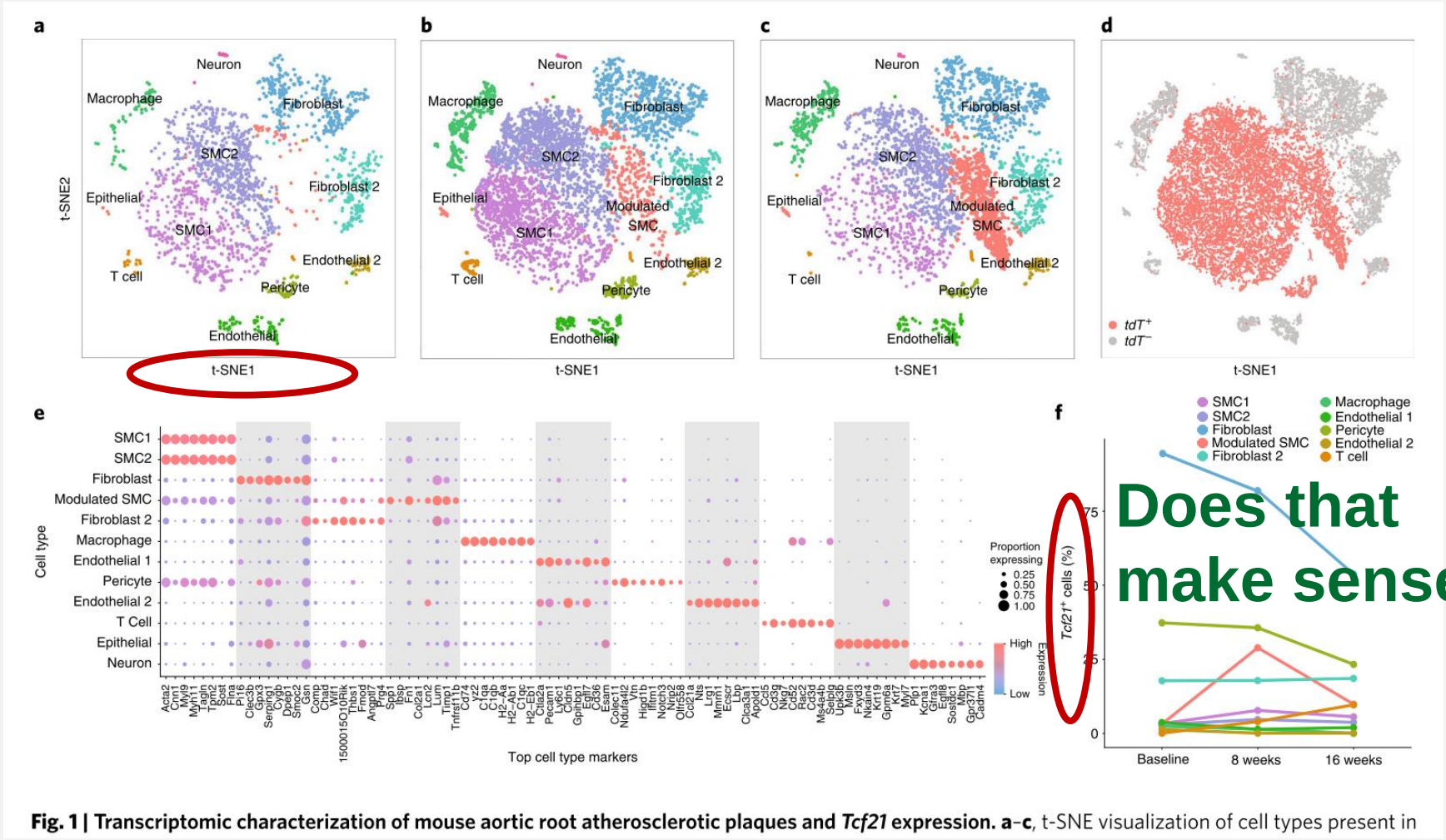
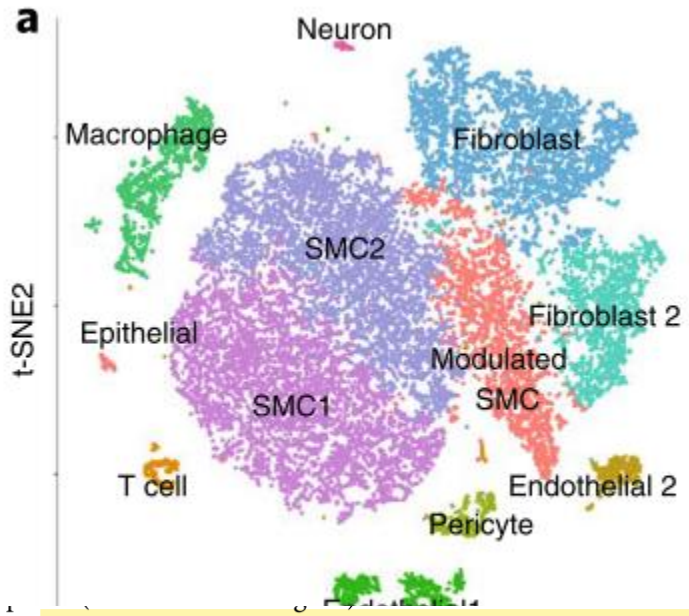
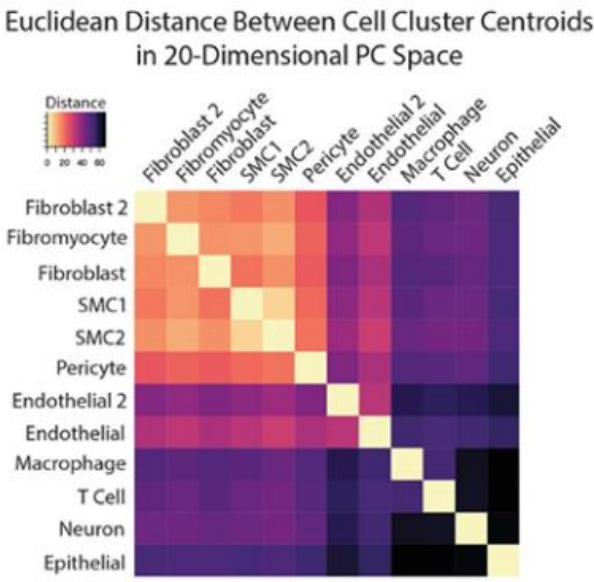


Fig. 1 | Transcriptomic characterization of mouse aortic root atherosclerotic plaques and *Tcf21* expression. a–c, t-SNE visualization of cell types present in

scRNA-seq

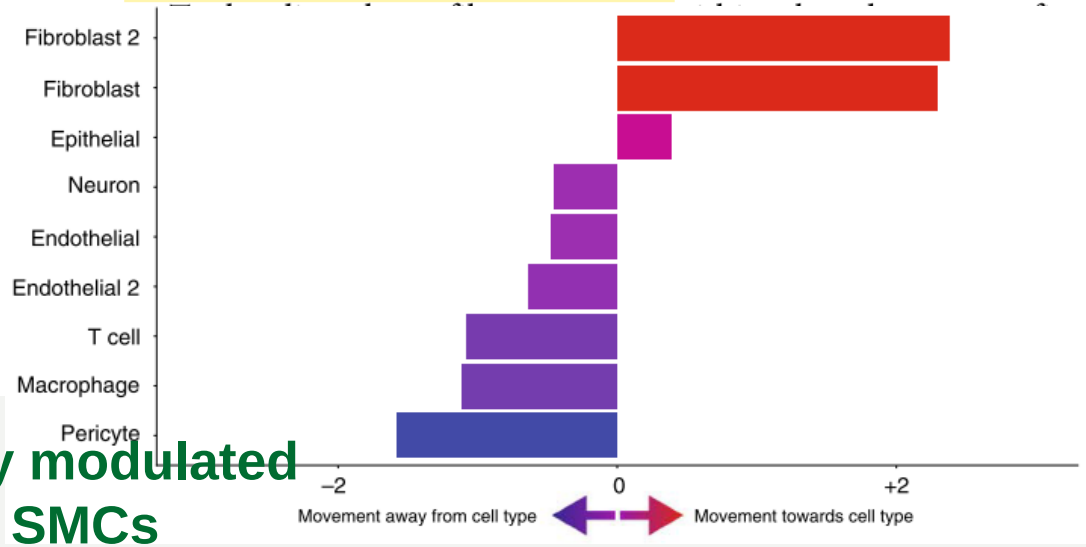




comprise an integrin heterodimer restricted to SMCs[20]. Given the clear transition to a fibroblast-like phenotype, and their separation from other cell clusters, we termed the modulated SMCs 'fibromyocytes', reflecting their origin from smooth muscle myocytes and their adoption of fibroblast phenotype.

Interestingly, using t-SNE visualization, the 'fibromyocyte' cluster appeared to be continuous with the fibroblast 2 population. Calculating Euclidean distance in 20-dimensional principal

lated SMCs were becoming more transcriptionally similar to other cell types within the lesion. We calculated the Euclidean distance between the centroids of all cell groups in 20-dimensional principal component space and determined, with contractile SMCs as a reference point, how the phenotypically modulated SMCs had shifted in relation to each cell cluster. This analysis revealed that during

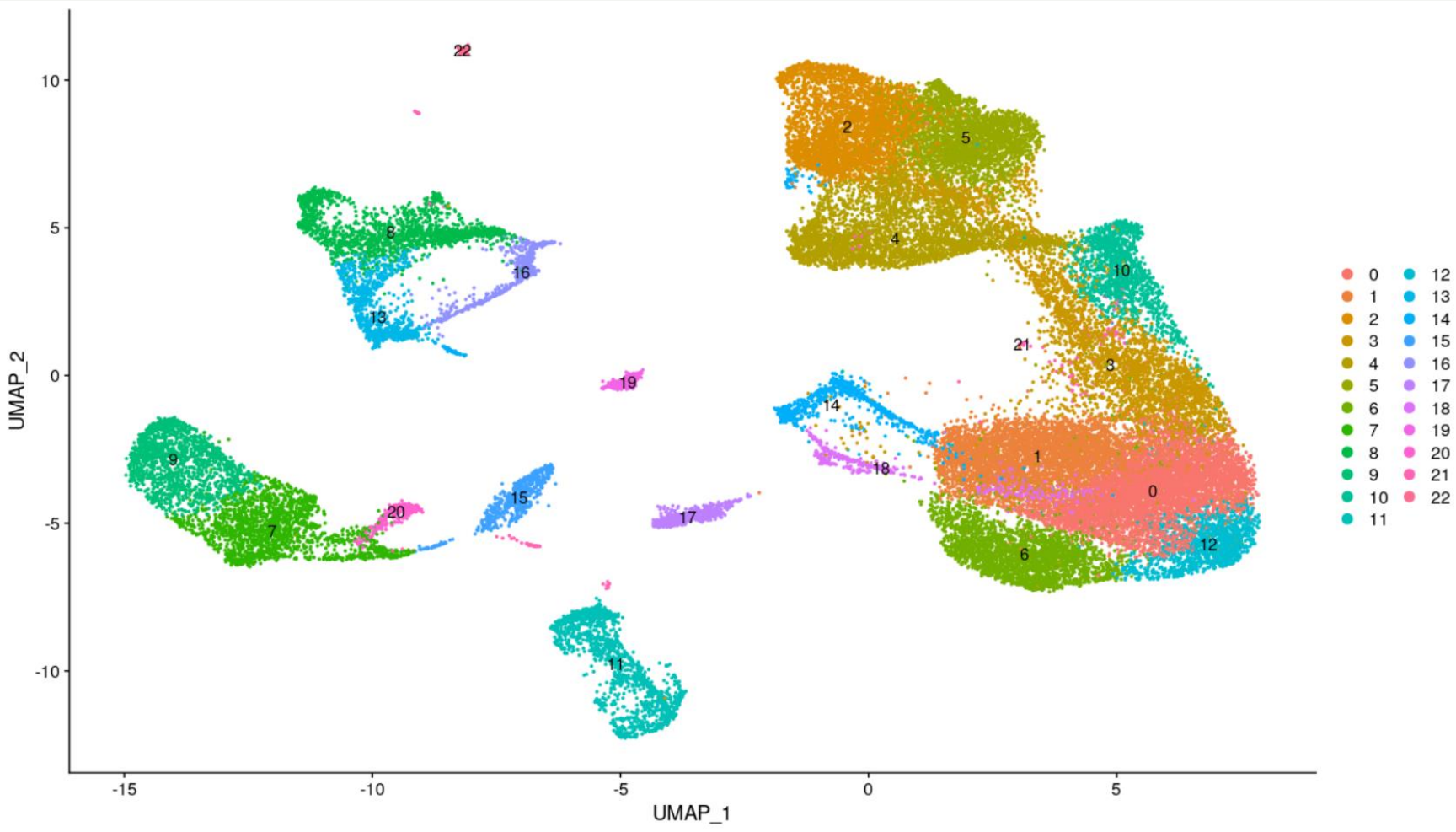


Contractile to phenotypically modulated SMCs, relative to contractile SMCs

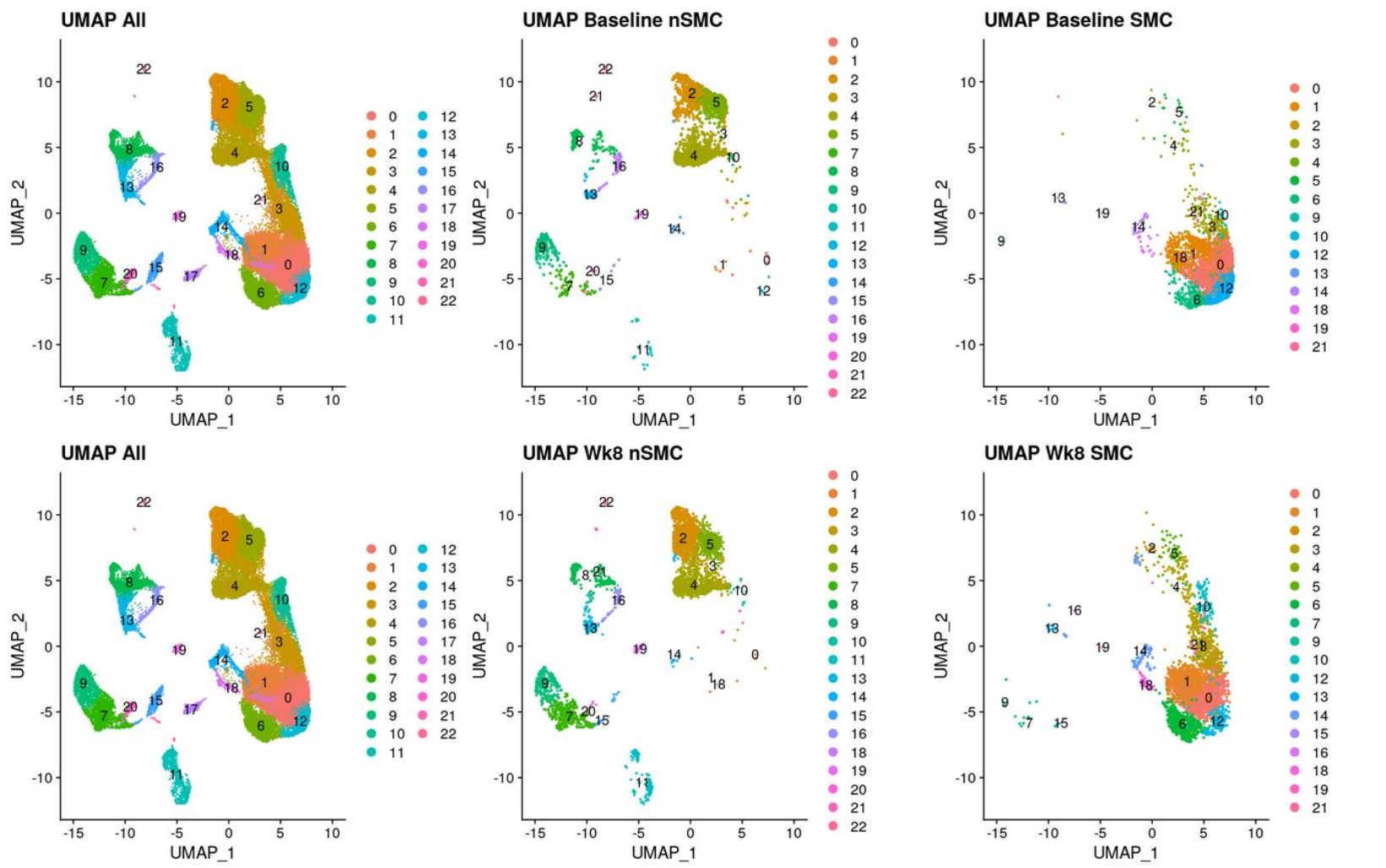
scRNA-seq

smc.baseline.counts	smc.wk8.counts	smc.wk16.counts	wtsmc.counts	wtnsmc.counts	nonsmc.baseline.counts	nonsmc.wk8.counts	nonsmc.wk16.counts	cluster
1376	841	541	*2758*	*25*	4	1	20	0
687	918	284	*1889*	*12*	6	4	2	1
3	19	8	*30*	*2028*	588	1040	400	2
259	458	673	*1390*	*172*	45	71	56	3
7	7	21	*35*	*2026*	895	862	269	4
17	51	11	*79*	*1531*	923	429	179	5
315	590	150	*1055*	*0*	0	0	0	6
0	13	2	*15*	*583*	72	382	129	7
0	0	1	*1*	*467*	133	278	56	8
1	3	2	*6*	*556*	186	258	112	9
16	91	701	*808*	*30*	8	10	12	10
0	0	1	*1*	*200*	19	178	3	11
932	186	28	*1146*	*3*	3	0	0	12
1	10	2	*13*	*290*	59	173	58	13
50	100	33	*183*	*31*	8	17	6	14
0	1	0	*1*	*30*	8	20	2	15
0	1	1	*2*	*227*	119	71	37	16
0	0	0	*0*	*0*	0	0	0	17
32	80	19	*131*	*2*	0	1	1	18
1	1	0	*2*	*79*	23	50	6	19
0	0	0	*0*	*18*	3	13	2	20
10	21	16	*47*	*41*	12	27	2	21
0	0	0	*0*	*84*	15	50	19	22
0	0	0	*0*	*0*	0	0	0	23
3707	**3391**	**2494**	**9592**	**8435**	**3129**	**3935**	**1371**	276

Do it ourselves …



scRNA-seq


UMAP All
UMAP Baseline nSMC
UMAP Baseline SMC
UMAP All
UMAP Wk8 nSMC
UMAP Wk8 SMC
UMAP_1
UMAP_2