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Published online: 26 Oct 2020.

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A bibliometric analysis of highly cited Phosphoinositide 3-Kinase (PI3K) research papers

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This study aimed to identify and analyze the characteristics of highly cited articles in phosphoinositide 3-kinase (PI3K) research using the Science Citation Index Expanded from 1900 to 2016. Altogether 1,922 highly cited papers in seven document types with cited at least 100 times since publication to the end of 2016 from Web of Science Core Collection were found, and a total of 1,556 highly cited articles were published from 1990 to 2014. The articles were analysed in terms of document type, language of publication, trends in publication, journals, Web of Science categories, and publications of countries, institutions, and authors. The results showed that *Journal of Biological Chemistry* led 211 journals. The top three categories were biochemistry and molecular biology, cell biology, and oncology. The USA took the lead position among 43 countries with 67% of all the highly cited articles, and Harvard University of the USA with 14% of all highly cited articles was the most productive institution. A comprehensive analysis of keywords revealed that activation, pathway, Akt, and apoptosis were recent foci. In addition, classic articles with more than 1,000 citations since publication to the end of 2016 are also discussed.

Keywords: *Scientometrics, Web of Science, Phosphoinositide 3-Kinase, PI3K, Front Page, Author Keywords, KeyWords Plus*

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1. Introduction

In 1990, a highly cited article entitled "Purification and characterization of phosphoinositide 3-kinase from rat liver" [1] was published by authors from Tufts University School of Medicine and Massachusetts General Hospital in the USA. Researches related to cancer were carried in

following years [2,3]. At the same time, Cantley [4] reported the signaling pathway phosphoinositide 3-kinase (PI3K) and elucidation of its role in tumor growth. Phosphatidylinositol 3-kinase pathway was one of the main research topics in following years, for example "Modulation of hypoxia-inducible factor 1α expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: Implications for tumor angiogenesis and therapeutics" [5]; "The phosphatidylinositol 3-kinase-AKT pathway in human cancer" [3]; "Exploiting the PI3K/AKT pathway for cancer drug discovery" [6]; "The protein kinase B/Akt signalling pathway in human malignancy" [7]; and "Targeting the phosphoinositide 3-kinase pathway in cancer" [8].

In this study, highly cited articles on phosphoinositide 3-kinase (PI3K) listed in the Science Citation Index Expanded were screened, and classic articles in terms of their total citations and their citations in recent year were identified and compared.

2. Materials And Methods

The data used in this study were retrieved from the Clarivate Analytics Web of Science, the online version of the Science Citation Index Expanded (SCI-EXPANDED) on 21 September 2017. The database was searched using the keywords "phosphoinositide 3-kinase" and "PI3K" in topic (title, abstract, author keywords, and *KeyWords Plus*) from 1900 to 2016. *KeyWords Plus* supplied additional search terms extracted from the titles of articles cited by authors in their bibliographies and footnotes in the ISI (now Clarivate Analytics) database, together with substantially augmented title-word and author-keyword indexing [9]. Another two filters, TC_{2016} and the 'front page', were also employed to retrieve related documents.

In this research, documents that were cited at least 100 times from Web of Science Core Collection ($TC_{2016} \geq 100$) were defined as highly cited documents [10,11], and the documents were classified as follows:

- TC_{2016} is the total number of times a document was cited from Web of Science Core Collection from its publication until the end of 2016 [12,13];
- C_0 is number of citations in a publication year [14];
- C_{2016} is the number of citations in the year 2016 [15];
- *TCPY* is the total citations per year [15]; and
- CPP_{2016} is total number of citations (TC_{2016}) per number of total publication (*TP*) ($CPP_{2016} = TC_{2016}/TP$).

The advantage of indicators such as TC_{2016} and CPP_{2016} is their invariance, as they are not updated as time goes on [16]. The 'front page', means that only the documents with searching keywords in their 'front page' - including the title, abstract, and author keywords - were preserved [16]. Documents were excluded if they could only be retrieved by *KeyWords Plus*.

In total 1,992 documents were regarded as highly cited documents. The records were downloaded and reorganized using Microsoft Excel 2013 [17]. The impact factor (IF_{2016}) of a journal was based on the *Journal Citation Report* 2016. In the SCI-EXPANDED database, the corresponding author was designated as the "reprint author" and but the term "corresponding author" is used in this study [18]. For a single-authored article where authorship was unspecified, the single-author was treated as both first and corresponding author. Similarly, for a single institution article, the institution was classified as both the first author's institution and the corresponding author's institution [19]. Only papers by the first corresponding author were considered in this study. Affiliations in England, Scotland, Northern Ireland, and Wales were reclassified as being from the United Kingdom (UK) [20]. Affiliations in the USSR were checked and reclassified to be in Lithuania. Affiliations in Hong Kong before 1997 were included with those from China [16].

3. Results and Discussion

3.1 *Document Type and Language of Publication*

In total 1,922 documents in seven document types were found to be highly cited ($TC_{2016} \geq 100$) phosphoinositide 3-kinase (PI3K) publications. Our analyses of these document types and their citations per publication followed the methods proposed earlier [21]. The most used document type was the article (81% of 1,922 documents) followed by reviews (18%) (Table 1). Editorial materials had the highest citations per publication (CPP_{2016}) with 463.

Lewis C. Cantley from Harvard Medical School and Division of Signal Transduction, published the most frequently cited editorial material entitled "The phosphoinositide 3-kinase pathway" [4] with TC_{2016} of 3,163. A review entitled "Specificity of receptor tyrosine kinase signaling: Transient versus sustained extracellular signal-regulated kinase activation" [22] was the most frequently cited publication in phosphoinositide 3-kinase (PI3K) research field with TC_{2016} of 3,858. "The phosphatidylinositol 3-kinase-AKT pathway in human cancer" [3] was also a highly cited review with TC_{2016} of 3,598.

The number of authors per publication (APP) for articles was higher than that of others. An article entitled "The genomic landscape of hypodiploid acute lymphoblastic leukemia" [23] had the most authors (63). All 1,556 articles were published in English.

3.2. Trends in Phosphoinositide 3-Kinase (PI3K) Publications

Only articles were selected for further analysis because they included whole research ideas and results [24]. Figure 1 shows the distribution of the 1,556 highly cited phosphoinositide 3-kinase (PI3K) articles over years and their citations per publication (CPP_{2016}) [25]. In 1990 only one article had the highest CPP_{2016}, which was entitled "Purification and characterization of phosphoinositide 3-kinase from rat liver" [1] with a TC_{2016} of 521. Figure 1 suggests that it takes CPPs about a decade to reach a plateau. Similarly, classic articles ($TC_{2010} \geq 1,000$) in the top-cited research works in the SCI-EXPANDED [26] as well as highly cited articles ($TC_{year} \geq 100$) in the dengue-related publications [27] and

research on Ebola [28] also took about ten years to reach a plateau. It would seem that at least one decade is needed to evaluate the impact of such papers [25].

3.3 *Journals and Web of Science Categories*

In total, 1,556 highly cited phosphoinositide 3-kinase (PI3K) articles were published in 211 journals and were listed in 48 Web of Science categories in SCI-EXPANDED in 2016. Of the 211 journals, 98 journals (46%) contained only one highly cited article, 34 (16%) contained two articles, and 15 (7.1%) journals contained three. The five core journals that published 33% of 1,556 highly cited articles were *Journal of Biological Chemistry* (209 articles; 13%), *Cancer Research* (102; 6.6%), *Proceedings of the National Academy of Sciences of the United States of America* (98; 6.3%), *Molecular and Cellular Biology* (64; 4.1%), and *Journal of Clinical Investigation* (53; 3.4%) with IF_{2016} of 4.125, 9.122, 9.661, 4.398, and 12.784 respectively. Among the 211 journals, the *CA-A Cancer Journal for Clinicians* had the highest IF_{2016} of 187.04 for only one article entitled "Angiogenesis inhibitors: Current strategies and future prospects" [29].

It is worth noting that some of the highly cited articles were also published in journals with low impact factors [30]. Thus, for example, the highly cited entitled "Transforming growth factor-beta signaling during epithelial-mesenchymal transformation: Implications for embryogenesis and tumor metastasis" [31] was published in *Cells Tissues Organs* with an IF_{2016} of 0.776.

Of the 48 Web of Science categories, 11 (23% of 48) contained only one highly cited article, four (8.3%) contained two, and five (10%) contained three articles. Sixty-three percent of the articles were published in journals in three Web of Science categories: biochemistry and molecular biology (559 articles; 36% of 1,556), cell biology (457; 29%), and oncology (328; 21%).

3.4 *Publications of Countries*

Seven indicators such as the total, independent, internationally collaborative, nationally collaborative, first author, corresponding author, and single author articles were used to examine the research performances for different countries. The contributions provided by different countries were estimated by the affiliation of at least one author connected to the articles. Of the 1,556 highly cited phosphoinositide 3-kinase (PI3K) articles, 1,063 (68% of 1,556 articles) articles were single-country articles, 493 (32%) articles were internationally collaborative articles, and 546 (35%) articles were nationally collaborative ones. Table 2 shows the top 11 countries ranked by number of articles and the seven indicators. Two North American countries, seven European countries, and two Asian countries were ranked in the top 11. The seven major industrialized countries of the world (G7) along with Switzerland were the top eight countries to publish related articles. The G7 were highly productive for total articles, 1,410 articles (91% of 1,556 articles) and 937 single country articles (88% of 1,063 single country articles). This domination in publication from the G7 countries is not surprising because this pattern has occurred in many medical-related

topics, for example, patent ductus arteriosus [21], stem cells [32], *Helicobacter pylori* [33], and human papillomavirus [34].

3.5 *Publications of Institutions*

Seven indicators, such as the total number of articles (*TP*), single-institution articles (*IP*), internationally collaborative articles (*ICP*), nationally collaborative articles (*NCP*), first-author articles (*FP*), corresponding-author articles (*RP*), and single-author articles (*SP*), were also used to compare the publication performance of different institutions. The contributions of institutions were defined by the affiliation of at least one author. Of the 1,556 highly cited phosphoinositide 3-kinase (PI3K) articles, 517 (33% of 1,556 articles) were articles from single institutions, 493 (32%) were internationally collaborative articles, and 546 (35%) articles were nationally collaborative ones.

Table 3 shows that among the top 10 institutions, Harvard University in the USA ranked top, followed distantly by Dana-Farber Cancer Institute and the University of Texas in USA. These findings are not surprising because this pattern has also occurred in classic articles published by American scientists [35] and in the highly cited publications in World War II [11]. However, both the first author and the corresponding author of the most frequently cited article was from the Dana-Farber Cancer Institute in USA. In the UK, the University of Dundee was the only one non-USA institute in these top 10 institutions.

3.6 *Publications of Authors*

The *Y*-index is related to the number of first author publications (*FP*) and corresponding author publications (*RP*). The *Y*-index combines two parameters (*j*, *h*), to assess both the publication potential and characteristics of the contribution as a single index. This indicator has been used to compare highly cited authors [36-39] and classic authors [35,40] in a specific field.

The *Y*-index is defined as [15,35,40]

$$j \; = \; FP + RP \tag{1}$$

$$h \; = \; \tan^{-1}\left(\frac{RP}{FP}\right) \tag{2}$$

where *j* is the publication potential which is a constant related to publication quantity, and *h* is publication characteristics which can describe the proportion of *RP* to *FP*. The greater the value of *j*, the more the contribution of the first author and corresponding author publications. Different values of *h* represent different proportions of corresponding author publications from first author publications. $h > 0.7854$ indicates more corresponding author publications; $h = 0.7854$ indicates the same number of first author and corresponding author publication; and $h < 0.7854$ indicates more first author publications. When $h = 0$, *j* is the number of first author publications, and $h = \pi/2$, *j* is the number of corresponding author publications.

Only 1,493 (96%) of 1,556 highly cited phosphoinositide 3-kinase (PI3K) articles had both first and corresponding author information in the Web of Science. These articles were analysed by Y-index. Figure 2 shows the Y-index (j, h) distribution of the top 41 authors with $j \geq 5$. j is a publication intensity constant: an author with a high j has more articles as the first or corresponding author, and takes the leadership role in more articles. L.C. Cantley, C.L. Arteaga, and D.M. Yellon published 10 corresponding author articles with ($10, \pi/2$). Similarly, P.P. Pandolfi with ($8, \pi/2$) had the same publication characteristics ($h = \pi/2$). However, Cantley, Arteaga, and Yellon had a higher publication potential with $j = 10$ than others with $j < 10$. G.B. Mills ($7, \pi/2$), W.R. Sellers ($7, \pi/2$), G. Thomas ($7, \pi/2$), R.A. Firtel ($7, \pi/2$), B. Vanhaesebroeck ($7, 1.406$), S. Dimmeler ($7, 1.190$), L. Stephens ($7, 0.9273$), J.R. Mcmullen ($7, 0.9273$), J.A. Engelman ($7, 0.6435$), and A.K. Gupta ($7, 0.6435$) had the same value of j. It is clear that all of these authors are located on the same curve ($j = 7$) in Fig. 4, indicating that they have the same publication potential but different publication characteristics. Mills, Sellers, Thomas, and Firtel published only corresponding author articles. Vanhaesebroeck ($h = 1.406$) has a higher ratio of corresponding author articles to first author articles, whereas Engelman ($h = 0.6435$) and Gupta ($h = 0.6435$) have a lower one. The Y-index shows that Stephens and Mcmullen had the same publication potential and publication characteristics with the same Y-index ($7, 0.9273$). In Fig. 2, 17 authors published only corresponding author article. Both J.J. Zhao and H.B. Zhang published the same number of first and corresponding author articles. Only five authors such as A.K. Gupta, J.A. Engelman, L.E. Rameh, S. Misra, and K. Ueki published more first author articles than corresponding author articles. K. Ueki had the lowest h of 0.2450, published only one corresponding author articles and four first author articles. A possible bias may occur when calculating the Y-index in that authors are sometimes listed in alphabetical order [35]. In such a case, the first author may not always be the major contributor to an article.

3.7 *Classic Articles*

In the 1970s, the most cited articles were labelled as "classic citations" by Garfield (1974). Articles with $TC_{year} \geq 1,000$ were also called classic articles by Ho's group [35,41,42]. Highly cited articles nevertheless provide an interesting and useful insight into which authors, articles, and topics are influencing the profession over time [43]. It is believed that Nobel Prize winners are consistently highly cited while only a small percentage of most-cited authors win the prize [44]. Table 4 presents the 11 classic phosphoinositide 3-kinase (PI3K) articles with $TC_{2016} \geq 1,000$. Of these 11 articles, three were published in 1997 and two in 1998 and 2004, respectively. The journals in which these classic articles were published were *Science* ($IF_{2016} = 37.205$) with four articles, *Cancer Research* ($IF_{2016} = 9.122$) and *Cell* ($IF_{2016} = 30.410$) with two articles, and one each in *Cancer Cell* ($IF_{2016} = 27.407$), *Current Biology* ($IF_{2016} = 8.851$), and *Genes & Development* ($IF_{2016} = 9.413$).

The 11 classic articles were published by 107 authors from 38 institutions located in nine countries including USA (25 institutions), the UK (3), Italy (3), Japan (2), and one institute is each of Israel, Canada, China, and Spain, Switzerland. Harvard University provided four classic articles without any first and corresponding authors. University of Texas

(1 first author article, 1 corresponding author article), University of Pennsylvania (1, 1), Beth Israel Deaconess Medical Center (0, 1), Dana-Farber Cancer Institute (1, 1), and Mc-Gill University (0, 0) published two classic articles respectively. Three of 107 classic authors such as L.C. Cantley from Harvard University, T.F. Franke from National Cancer Institute in USA, and D.R. Kaplan from McGill University in Canada had two classic articles. In the 2017 Clarivate Citation Laureates, (https://en.wikipedia.org/wiki/Clarivate_Citation_Laureates) Lewis C. Cantley was selected among possible Nobel Prize winners in physiology or medicine for his discovery of the signaling pathway phosphoinositide 3-kinase (PI3K) and elucidation of its role in tumor growth.

The article entitled "*MET* amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling" [45] by Engelman and other 18 authors from USA, Japan, Italy, and China, had the highest total number of citations with TC_{2016} of 2,273 and second impact in 2016 with C_{2016} of 259. This was the one classic article by Cantley. The other, "Direct regulation of the Akt proto-oncogene product by phosphatidylinositol-3,4-bisphosphate" was by Franke et al. [46] with TC_{2016} of 1,119.

The citation lives of classic articles with $TC_{year} \geq 1,000$ in research fields of psychology [42] were recently reported. The citation lives of the 11 classic phosphoinositide 3-kinase (PI3K) articles are shown in Fig. 2. The articles with the highest TC_{2016} can be considered the most popular articles in phosphoinositide 3-kinase (PI3K) research. In general, only the trends of two classic articles by Engelman et al. in 2007 and Levental et al. in 2009 have kept on increasing since their publication years, while the other's slopes climbed initially toward a plateau.

Highly cited articles may not always be in high impact positions [15]. Thus Fig. 3 shows the top nine high impact articles ($C_{2016} \geq 100$) in 2016 and their citation lives. The articles with higher C_{2016} are considered to have most impact in recent years. Recently published articles, for example, "Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies" [47] have great potential, but they do not have a high $TC_{2016} \geq 1,000$ as a classic article because the time span is too short to accumulate a large number of citations.

A total of 497 highly cited articles (32% of 1,556 articles) had no citations from Web of Science Core Collection in the publication year ($C_0 = 0$) but 12 articles (0.77%) had at least 30 ($C_0 > 30$) including three articles in 2014, two in 1997 and 1998, and one in 1994, 2005, 2006, 2007, and 2009 respectively. The articles "MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling" [45] and "mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt" [48] were the only two ranked in the top ten for the categories of TC_{2016}, C_{2016}, and C_0.

3.8 Research Tendencies and Hotspots

The distribution of words in article titles, abstracts, author keywords, and *KeyWords Plus* can be informative when evaluating trends in research topics [49,50]. Table 5 shows the top ten key words provided in each of the abstracts, author keywords, and *KeyWords Plus* for the articles analysed in this study. Ninety-six journals had no author keywords,

including some with high impact, for example *CA-A Cancer Journal for Clinicians* (IF_{2016} = 187.04), *New England Journal of Medicine* (IF_{2016} = 72.406), *Nature Reviews Molecular Cell Biology* (IF_{2016} = 46.602), *Nature Biotechnology* (IF_{2016} = 41.667), *Nature* (IF_{2016} = 40.137), *Science* (IF_{2016} = 37.205), *Lancet Oncology* (IF_{2016} = 33.9), and *Cell* (IF_{2016} = 30.41).

The results of our keyword analyses provide information about the main and possible research foci as each word cluster comprised several supporting words. Thus the possible main research foci in phosphoinositide 3-kinase (PI3K) research are activation, pathway, Akt, and apoptosis with the most highly cited articles. "Activation" (activate, activated, activates, activating, activation, and activator), "pathway" (pathway and pathways), "Akt" (Akt, Akt1, Akt2, and Akt3), and "apoptosis" (antiapoptosis, antiapoptotic, apoptosis, apoptotic, and proapoptotic) grouped respectively. Figure 5 compares the distributions of these four main focuses in phosphoinositide 3-kinase (PI3K) research. The earliest highly cited articles of activation, pathway, Akt, and apoptosis were found to be in 1991, 1991, 1996, and 1996 respectively. The article "MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling" by Engelman et al. [45] was the most highly cited article related to "activation" and "pathway" with TC_{2016} of 2273. "Regulation of neuronal survival by the serine-threonine protein kinase Akt" by Dudek et al. [51](1997) was the most highly cited article related to "Akt" with TC_{2016} of 1867 and "Interleukin-3-induced phosphorylation of BAD through the protein kinase Akt" by Delpeso et al. [51] was the most highly cited article related to "apoptosis" with TC_{2016} of 865.

4. Summary

A total of 1,556 phosphoinositide 3-kinase (PI3K) highly cited articles were published from 1990 to 2014. English was the only language used. The *Journal of Biological Chemistry*, *Cancer Research*, and *Proceedings of the National Academy of Sciences of the United States of America* published the most highly cited articles. Three leading Web of Science categories were biochemistry and molecular biology, cell biology, and oncology. The USA published most articles followed distantly by the UK and Japan. The G7 were highly productive for total articles, ranked in the top nine. Harvard University ranked top among all the indicators of research in this area. The results from the *Y*-index showed that L.C. Cantley, C.L. Arteaga, and D.M. Yellon had the highest potential to publish highly cited articles. L.C. Cantley also published the most corresponding author articles while K. Ueki, A.K. Gupta, J.A. Engelman, and C.L. Carpenter published the most first author articles. Eleven classic articles were found that were cited at least 1,000 times since publication to the end of 2016. "Activation", "pathway", "Akt", and "apoptosis" were the four main keywords in phosphoinositide 3-kinase (PI3K) research.
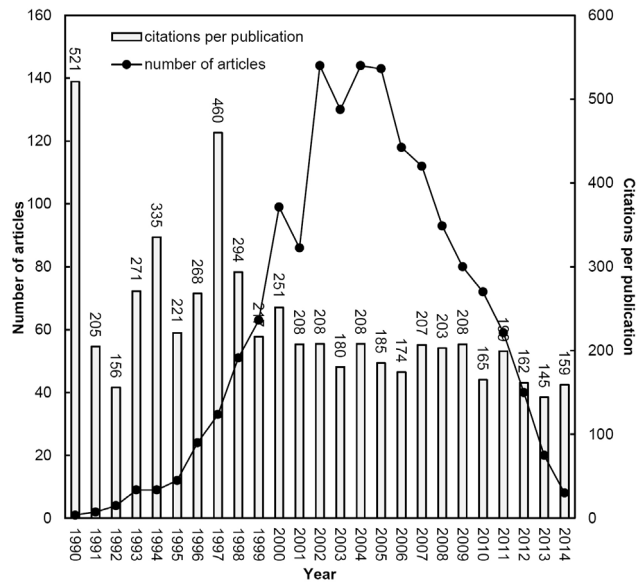
Figure 1

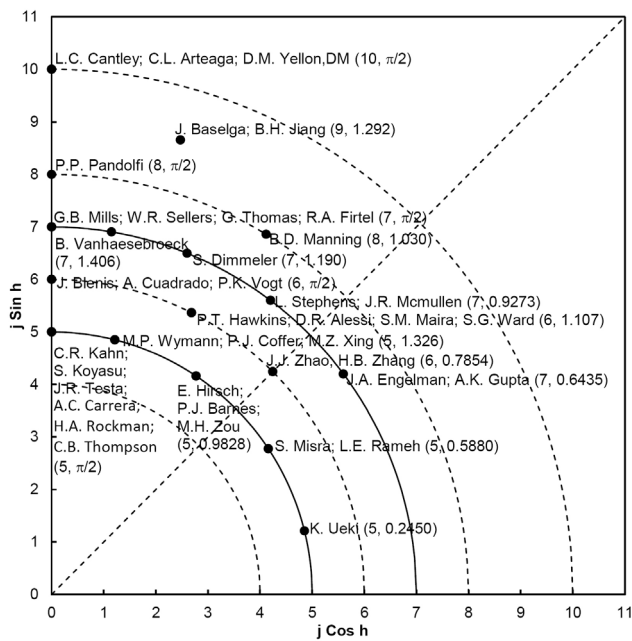**Trends of highly cited articles and citations per publication from 1990 to 2016.**

Figure 2

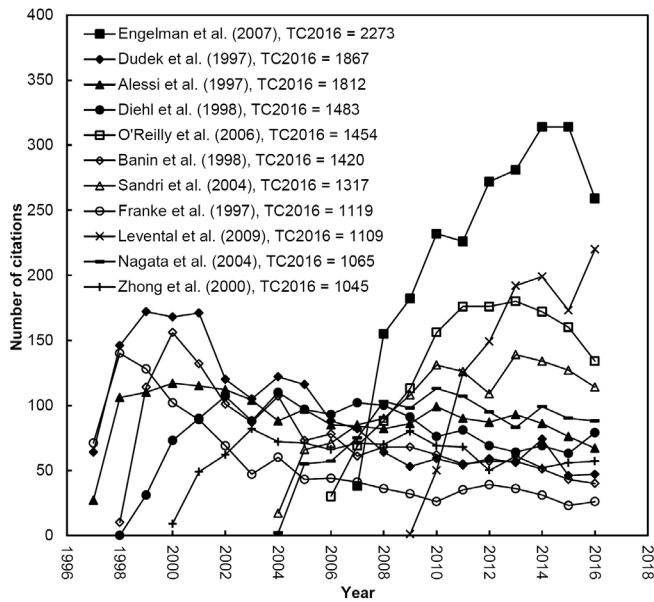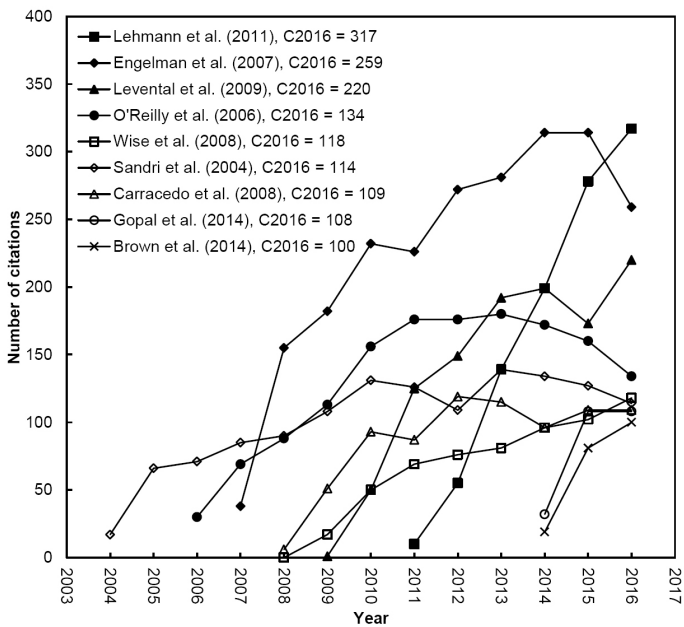**Distribution of the top 41 authors with their Y-index values ($j \geq 5$)**

Figure 3

The lives of the ten classic articles.

Figure 4

The lives of the top nine impact cited articles in 2016 ($C_{2016} \geq 100$).
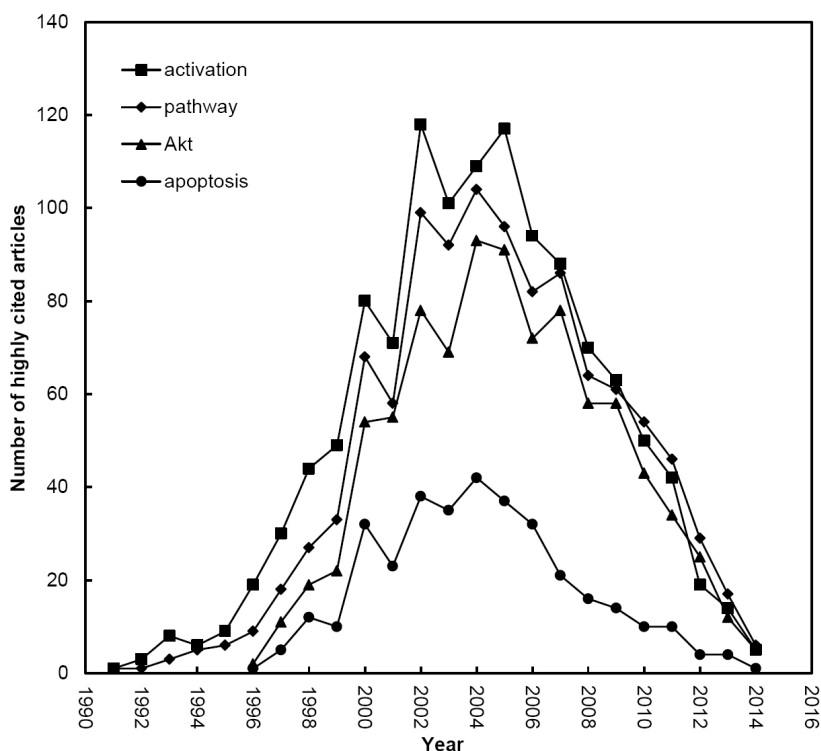
Figure 5

Distributions of research focuses during 1991-2014

Table 1

Citations and authors according to document type.

Document type	*TP*	%	TC_{2016}	CPP_{2016}	*AU*	*APP*
Article	1556	81	326097	210	12062	7.8
Review	349	18	100151	287	1165	3.3
Proceedings paper	35	1.8	5823	166	144	4.1
Editorial material	12	0.62	5557	463	27	2.3
Note	5	0.26	1206	241	21	4.2
Book chapter	4	0.21	873	218	11	2.8
Retracted publication	1	0.052	105	105	11	11

TP: number of articles; *AU*: number of authors; *APP*: number of authors per publication (*AU/TP*); TC_{2016}: total citations since publication to the end of 2016; CPP_{2016} citations per paper (TC_{2016}/TP).

Table 2
Top 11 countries with at least 45 articles

Country	TP	TPR (%)	IPR (%)	ICPR (%)	NCPR (%)	FPR (%)	RPR (%)	SPR (%)
USA	1036	1 (67)	1 (63)	1 (73)	1 (65)	1 (58)	1 (58)	1 (50)
UK	225	2 (14)	2 (9.7)	2 (25)	2 (7.1)	2 (10)	2 (10)	2 (29)
Japan	129	3 (8.3)	3 (5.7)	6 (14)	3 (6.6)	3 (5.0)	3 (4.9)	N/A
Germany	103	4 (6.6)	4 (2.9)	3 (15)	4 (3.3)	4 (3.4)	4 (3.5)	3 (7.1)
Canada	95	5 (6.1)	6 (2.4)	4 (14)	6 (2.0)	5 (3.3)	5 (3.2)	3 (7.1)
Switzerland	87	6 (5.6)	8 (1.7)	5 (14)	11 (1.1)	8 (2.1)	9 (2.1)	N/A
Italy	76	7 (4.9)	10 (1.1)	7 (13)	10 (1.3)	9 (2.1)	8 (2.1)	N/A
France	72	8 (4.6)	5 (2.8)	8 (8.5)	5 (3.1)	6 (3.1)	6 (2.9)	3 (7.1)
Spain	67	9 (4.3)	6 (2.4)	8 (8.5)	6 (2.0)	7 (2.5)	7 (2.7)	N/A
China	45	10 (2.9)	12 (1.0)	10 (6.9)	12 (0.73)	10 (1.7)	10 (1.9)	N/A
Netherlands	45	10 (2.9)	12 (1.0)	10 (6.9)	12 (0.73)	11 (1.5)	11 (1.5)	N/A

TP: total number of articles; TPR (%), IPR (%), ICPR (%), NCPR (%), FPR (%), RPR (%), and SPR (%): the rank and percentage of total articles, single-country articles, internationally collaborative articles, nationally collaborative articles, first-author articles, corresponding-author articles, and single-author articles among their total articles, respectively.

Table 3
Top 10 institutions with at least 35 articles

Institution	TP	TPR (%)	IPR (%)	ICPR (%)	NCPR (%)	FPR (%)	RPR (%)	SPR (%)
Harvard University, USA	214	1 (14)	1 (4.8)	1 (16)	1 (20)	1 (4.9)	1 (4.7)	1 (14)
Dana-Farber Cancer Institute, USA	52	2 (3.3)	87 (0.19)	9 (3.4)	2 (6.2)	4 (1.7)	3 (1.9)	N/A
University of Texas, USA	52	2 (3.3)	2 (3.3)	6 (3.9)	9 (2.9)	2 (2.2)	2 (2.3)	N/A
University of Pennsylvania, USA	49	4 (3.1)	5 (2.1)	14 (2.6)	3 (4.6)	3 (1.8)	4 (1.7)	N/A
Memorial Sloan Kettering Cancer Center, USA	42	5 (2.7)	7 (1.7)	5 (4.1)	11 (2.4)	7 (1.4)	7 (1.4)	N/A
Beth Israel Deaconess Medical Center, USA	41	6 (2.6)	N/A	12 (3.2)	3 (4.6)	12 (1.0)	13 (1.0)	2 (7.1)
University of California, San Francisco, USA	41	6 (2.6)	15 (1.0)	3 (5.1)	15 (2.0)	11 (1.1)	11 (1.1)	N/A

Contd...

Massachusetts General Hospital, USA	38	8 (2.4)	87 (0.19)	7 (3.7)	6 (3.5)	18 (0.84)	11 (1.1)	2 (7.1)
University of Dundee, UK	36	9 (2.3)	3 (2.5)	14 (2.6)	17 (1.8)	5 (1.5)	5 (1.5)	N/A
University of California, San Diego, USA	35	10 (2.2)	4 (2.3)	26 (2.0)	11 (2.4)	5 (1.5)	5 (1.5)	N/A

TP: total number of articles; *TPR* (%), *IPR* (%), *ICPR* (%), *NCPR* (%), *FPR* (%), *RPR* (%), and *SPR* (%),: the rank and percentage of total articles, single-institution articles, internationally collaborative articles, nationally collaborative articles, first-author articles, corresponding-author articles, and single-author articles among their total articles, respectively; N/A: not applicable.

Table 4

Eleven classic phosphoinositide 3-kinase (PI3K) articles ($TC_{2016} \geq 1,000$) in Science Citation Index Expanded

Rank (TC_{2016})	Rank (C_{2016})	Article title	Reference
1 (2273)	2 (259)	*MET* amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling	Engelman et al. [45]
2 (1867)	85 (47)	Regulation of neuronal survival by the serine-threonine protein kinase Akt	Dudek et al. [51]
3 (1812)	36 (67)	Characterization of a 3-phosphoinositide-dependent protein kinase which phosphorylates and activates protein kinase Bα	Alessi et al. [52]
4 (1483)	20 (79)	Glycogen synthase kinase-3β regulates cyclin D1 proteolysis and subcellular localization	Diehl et al. [53]
5 (1454)	4 (134)	mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt	O'Reilly et al. [48]
6 (1420)	122 (40)	Enhanced phosphorylation of p53 by ATN in response to DNA damage	Banin et al. [54]
7 (1317)	6 (114)	Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy	Sandri et al. [55]
8 (1119)	250 (26)	Direct regulation of the Akt proto-oncogene product by phosphatidylinositol-3,4-bisphosphate	Franke et al. [46]
9 (1109)	3 (220)	Matrix crosslinking forces tumor progression by enhancing integrin signaling	Levental et al. [56]
10 (1065)	14 (88)	PTEN activation contributes to tumor inhibition by trastuzumab, and loss of PTEN predicts trastuzumab resistance in patients	Nagata et al. [57]
11 (1045)	55 (57)	Modulation of hypoxia-inducible factor 1α expression by the epidermal growth factor/phosphatidylinositol 3-kinase/PTEN/AKT/FRAP pathway in human prostate cancer cells: Implications for tumor angiogenesis and therapeutics	Zhong et al. [5]

TC_{2016}: number of citations from publication to the end of 2016; C_{2016}: number of citations in 2016 only.

Table 5
Top ten used keywords

Words in title	*TP* (%)	Word in abstract	*TP* (%)	Author keywords	*TP* (%)	*KeyWords Plus*	*TP* (%)
3-kinase	313 (20)	PI3K	1129 (73)	Akt	77 (15)	Phosphatidylino-sitol 3-kinase	330 (21)
signaling	307 (20)	cells	966 (62)	apoptosis	55 (11)	activation	318 (21)
Akt	276 (18)	activation	880 (57)	PI3K	54 (11)	expression	197 (13)
cells	274 (18)	cell	866 (56)	PTEN	34 (6.7)	phosphorylation	159 (10)
activation	245 (16)	kinase	860 (55)	Phosphoinositide 3-kinase	27 (5.3)	Phosphoinositide 3-kinase	142 (9.2)
pathway	240 (15)	signal-ing	836 (54)	signal transduc-tion	27 (5.3)	pathway	127 (8.2)
kinase	234 (15)	protein	802 (52)	Phosphatidylino-sitol 3-kinase	21 (4.1)	signal-transduc-tion	123 (7.9)
cell	220 (14)	pathway	789 (51)	MTOR	19 (3.7)	protein-kinase	115 (7.4)
phosphoinositide	204 (13)	Akt	778 (50)	NF-kappa B	19 (3.7)	kinase	113 (7.3)
phosphatidylino-sitol	185 (12)	3-kinase	759 (49)	Cancer	18 (3.6)	in-vivo	111 (7.2)

TP: total number of article

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