The top cited articles on glioma stem cells in Web of Science

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Abstract

BACKGROUND: Glioma is the most common intracranial tumor and has a poor patient prognosis. The presence of brain tumor stem cells was gradually being understood and recognized, which might be beneficial for the treatment of glioma.

OBJECTIVE: To use bibliometric indexes to track study focuses on glioma stem cell, and to investigate the relationships among geographic origin, impact factors, and highly cited articles indexed in Web of Science.

METHODS: A list of citation classics for glioma stem cells was generated by searching the database of Web of Science-Expanded using the terms “glioma stem cell” or “glioma, stem cell” or “brain tumor stem cell”. The top 63 cited research articles which were cited more than 100 times were retrieved by reading the abstract or full text if needed. Each eligible article was reviewed for basic information on subject categories, country of origin, journals, authors, and source of journals.

Inclusive criteria: (1) articles in the field of glioma stem cells which was cited more than 100 times; (2) fundamental research on humans or animals, clinical trials and case reports; (3) research article; (4) year of publication: 1899–2012; and (5) citation database: Science Citation Index-Expanded.

Exclusive criteria: (1) articles needing to be manually searched or accessed only by telephone; (2) unpublished articles; and (3) reviews, conference proceedings, as well as corrected papers.

RESULTS: Of 2 040 articles published, the 63 top-cited articles were published between 1992 and 2010. The number of citations ranged from 100 to 1 754, with a mean of 280 citations per article. These citation classics came from nineteen countries, of which 46 articles came from the United States. Duke University and University of California, San Francisco led the list of classics with seven papers each. The 63 top-cited articles were published in 28 journals, predominantly Cancer Research and Cancer Cell, followed by Cell Stem Cell and Nature.

CONCLUSION: Our bibliometric analysis provides a historical perspective on the progress of glioma stem cell research. Articles originating from outstanding institutions of the United States and published in high-impact journals are most likely to be cited.

Key Words
Neural regeneration; reviews; brain glioma; stem cells; glioma stem cells; cancer stem cells; literature analysis; Web of Science; bibliometrics; citation; neuroregeneration
INTRODUCTION

Glioma is the most common intracranial tumor and accounts for about 45% of all intracranial tumors. A classification survey carried out by a multi-center study has shown that, in 2006, the incidence of primary brain tumors was 22.52/100,000, and glioma accounted for 29.78%\[^1\]. The common clinical treatments for patients with glioma are surgery and/or radiotherapy, chemotherapy. Patient prognosis is poor, and the average survival time of patients is only 18 months\[^2\]. Thus, the study of glioma is an urgent topic in cancer research.

Accumulation of genetic variation within normal cells is generally believed to lead to tumor development. Tumor cells are not homogeneous; they differ in morphology, proliferation and tumorigenicity after transplantation into immunodeficient mice\[^3\]. As early as the 1930s, scholars indicated that a glioma is derived from glial cells in subependymal zone\[^4\]. By the 1970s, scholars used the chemical carcinogen N-ethyl-N-nitrosourea to induce late pregnancy and successfully produced brain tumors in young rats\[^5\]. In the 1990s, in a detailed study of neural stem cells, it was suggested that nestin-positive cells enriched in the subependymal zone were neural stem cells\[^6\]. Nestin expression can be found in neural stem cells and precursor cells as well as tumor nerve cells, which suggested that these cells have an embryonic link.

Lapidot et al\[^7\] used CD34-positivity and CD38-negativity as specific cell surface markers to isolate continuously self-proliferating cells. These cells from patients with leukemia maintained their malignant potential and were named acute myelogenous leukemia stem cells. This was the first indication of the presence of human tumor stem cells. Recht et al\[^8\] used the N-ethyl-N-nitrosourea tumorigenic model, and used nestin as a marker to study the origin of glioma. This indirectly confirmed that brain tumors were derived from neural stem cells.

In 2003, Al-Hajj et al\[^9\] used a non-obese diabetic/severe combined immunodeficiency mouse model and successfully isolated human breast cancer stem cells using cell surface markers. In the same year, Singh et al\[^9\] isolated a subset of cells with unlimited proliferative and differentiation potential from 14 patients with different types of gliomas. This subset of cells has different cellular and genetic characteristics compared with common brain tumor cells. They express the neural stem cell markers such as nestin, musashi-1, Bmi-1 and CD133, and have a greater ability for self-renewal and proliferation than a neural stem cell. The cell subset could differentiate into tumor cells with the same phenotype as the source tumor in vitro and in vivo. They are considered to be a kind of tumor stem cells.

Glioma stem cells are a small subset of glioma cells that cause tumors, and maintain tumor growth and heterogeneity. They are in a dormant state under normal circumstances. Under appropriate conditions, cancer stem cells can differentiate into new tumor cells, which are regarded as the source of tumorigenesis, tumor recurrence and metastasis. Gliomas display infiltrative growth, and cannot be completely removed surgically. Glioma stem cells are resistance to radiotherapy and chemotherapy. Therefore, if most of the glioma cells are eliminated, the tumor is still faced with the possibility of recurrence, and will have more resistance to treatment.

It is widely accepted that publications represent an important academic achievement of a research. Citation rating is a popular method to evaluate the impact of an investigator or a publication in the scientific community. Citations have important implications for authors, journals, and institutions\[^10\]. A higher citation for an article often signifies widely spreading or recognition in a particular area of research. Although there are obvious disadvantages in assessing the quality of a study simply based on the citation rating, it is widely accepted that this is the best method currently available for judging the merit of a paper or a journal\[^11\]. Citation analysis is also a feasible tool to recognize the research advances in the past and future research trends in a specific field.

Presently, various specialties have attempted to seek for “citation classics” or the most commonly cited articles in their fields\[^12\-13\].

To systematically review the citation classics dedicated to glioma stem cell research, we conducted the current study to focus exclusively on the top-cited articles in the Web of Science in an attempt to provide a bibliometric perspective of the progress in glioma stem cell research. We also intended to identify factors that contributed to a successful citation, such as journals in which the articles were published, the geographic origin of authors, as well as the institution and the related countries.
DATA SOURCES AND METHODOLOGY

Data retrieval
The database of the Institute for Web of Science Expanded citation index (1899 to 2012) was searched using the terms “glioma stem cell” or “glioma, stem cell” or “brain tumor stem cell” to identify “citation classics” categorized as those articles cited more than 100 times. “Document type” was applied to limit the format of publications. Papers published as “article” were selected for further analysis. Each article on the list was reviewed by reading the abstract first, and only studies dedicated to research on glioma stem cells were selected for further analysis. The following information was listed: authors, number of citations, year of publication, country of origin, institution, journal, and study types. All electronic searches were conducted on 15 February 2013.

Inclusion criteria
1. Papers in the field of glioma stem cells.
2. Articles with more than 100 citations.
3. Literature type: article.
4. Year of publication: 1899 to present.
5. Citation databases: Science Citation Index Expanded.
6. Fundamental research on humans and animals, clinical trials and case reports.

Exclusion criteria
We excluded articles that required manual searching or telephone access. We also excluded documents that were not published in the public domain, a number of reviews, conference proceedings, and corrected papers. The selection process of articles was shown in Figure 1.

RESULTS
A total of 2,040 papers were identified in the initial search for the period from 1899 to 2012, with 1,620 classified as “article” and 420 classified as “review, conference proceedings, as well as corrected papers”. Among them, 1,528 articles were cited more than once, and 63 articles were cited more than 100 times. As to the subject categories, of the top 63 cited articles, 22 articles were related to cell biology, 20 to oncology, eight to neurology, five to biochemistry and molecular biology, and the rest to other areas of biology.

Of the top 63 cited articles, the mean number of citations was 280 (range 101–754) and seven papers were cited more than 500 times (Table 1).

| Title                                                                 | Publication year | Total citation | Average per year |
|----------------------------------------------------------------------|-----------------|----------------|------------------|
| Identification of a cancer stem cell in human brain tumors            | 2003            | 1,754          | 159.45           |
| Glioma stem cells promote radioresistance by preferential activation of the DNA damage response | 2006            | 1,452          | 181.50           |
| Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma | 2004            | 861            | 86.10            |
| Molecular subclasses of high-grade glioma predict prognosis, delineate a pattern of disease progression, and resemble stages in neurogenesis | 2006            | 670            | 83.75            |
| A perivascular niche for brain tumor stem cells                      | 2007            | 662            | 94.57            |
| Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRα, IDH1, EGFR, and NF1 | 2010            | 577            | 144.25           |
| Tumor stem cells derived from glioblastomas cultured in basic fibroblast growth factor and epidermal growth factor more closely mirror the phenotype and genotype of primary tumors than do serum-cultured cell lines | 2006            | 570            | 71.25            |

Four of the seven papers were published in Cancer Cell, two in Cancer Research, and one in Nature. This showed that Cancer Cell is the core journal in the field of glioma stem cells. Cancer Cell was established in February.
2002 and the current editor-in-chief is Li-Kuo Su. The top 63 articles were published between 1992 and 2010, of which approximately 62% were published after 2004 (Figure 2).

![Figure 2] Frequency distribution showing publication years of the 63 top-cited articles.

Articles on glioma stem cells that gained greater than 100 citations were first observed in 1992, which increased in 2002, then steadily increased after a drop in 2003, and reached peaks between 2007 and 2009. However, in 2010, the number of articles gaining greater than 100 citations decreased sharply.

The 63 top-cited articles originated from nineteen countries, of which the United States with 46 articles is without doubt the most prolific. This is followed by Germany with six articles, and Canada and Italy, with four articles (Table 2).

### Table 2 Countries of origin of the top 63 cited articles on glioma stem cells

| Country       | Number of articles | % of 63 articles |
|---------------|--------------------|------------------|
| United States | 46                 | 73.02            |
| Germany       | 6                  | 9.52             |
| Canada        | 4                  | 6.35             |
| Italy         | 4                  | 6.35             |
| Japan         | 3                  | 4.76             |
| The Netherlands | 3                  | 4.76             |
| Spain         | 3                  | 4.76             |
| United Kingdom | 2                  | 3.18             |
| Switzerland   | 2                  | 3.18             |
| Australia     | 1                  | 1.59             |
| Austria       | 1                  | 1.59             |
| Belgium       | 1                  | 1.59             |
| Israel        | 1                  | 1.59             |
| Luxembourg    | 1                  | 1.59             |
| Norway        | 1                  | 1.59             |
| China         | 1                  | 1.59             |
| Scotland      | 1                  | 1.59             |
| South Korea   | 1                  | 1.59             |
| Sweden        | 1                  | 1.59             |

Given that some articles were authored with multiple sources of origin, especially those in the form of international research collaborations, the country of origin was defined by the address of the corresponding author. The leading institutions are shown in Table 3.

### Table 3 Top 11 institutions with publications on glioma stem cells

| Institution                                                                 | Number of articles | % of 63 articles |
|----------------------------------------------------------------------------|--------------------|------------------|
| Duke University                                                            | 7                  | 11.11            |
| University of California, San Francisco                                    | 7                  | 11.11            |
| Harvard University                                                          | 5                  | 7.94             |
| Memorial Sloan-Kettering Cancer Center                                     | 5                  | 7.94             |
| National Cancer Institute                                                  | 5                  | 7.94             |
| Dana-Farber Cancer Institute                                               | 4                  | 6.35             |
| Cedars Sinai Medical Center                                                | 3                  | 4.76             |
| Columbia University                                                        | 3                  | 4.76             |
| National Institutes of Health                                              | 3                  | 4.76             |
| National Institute of Neurological Disorders                               | 3                  | 4.76             |
| and Glioma stem cells                                                      |                    |                  |
| University of Toronto                                                      | 3                  | 4.76             |

Duke University and University of California, San Francisco were found to be the most productive institutions, with seven articles each, accounting for 11.11% of 63 top-cited articles. This was followed by Harvard University, Memorial Sloan-Kettering Cancer Center, and the National Cancer Institute with five articles each. The top three universities or institutions that publish papers on glioma stem cells are mainly located in the United States. Except for the United States institutions, the most active university among the top 11 Institution was University of Toronto in Canada, with three published studies. No Chinese institution was indexed in the list.

The 63 top-cited articles were published in 28 journals, predominantly in Cancer Research (n = 14) and Cancer Cell (n = 11), followed by Cell Stem Cell (n = 4) and Nature (n = 4) (Table 4).

### Table 4 Journals in which the top 63 cited articles on glioma stem cells were published (more than two articles)

| Journal                  | Impact factor | Number of articles |
|--------------------------|---------------|-------------------|
| Cancer Research          | 7.856         | 14                |
| Cancer Cell              | 26.566        | 11                |
| Cell Stem Cell           | 25.421        | 4                 |
| Nature                   | 36.290        | 4                 |
| Oncogene                 | 6.373         | 3                 |
| Gila                     | 4.820         | 2                 |
| Journal of Clinical Oncology | 18.372 | 2                 |
| Journal of Neuroscience  | 7.115         | 2                 |
| Neuron                   | 14.736        | 2                 |
| Gene Therapy             | 3.710         | 2                 |
Table 5 presents a list of the most productive authors, indicating that Rich JN authored seven articles, followed by Mclendon RE (six articles), and Fine HA, Hjelmeland AB, and Ligon KL, with four articles each.

| Author          | Institution             | Number of articles | First author | Corresponding author |
|-----------------|-------------------------|--------------------|--------------|----------------------|
| Rich JN         | Duke University         | 7                  | 4            |                      |
| Mclendon RE     | Duke University         | 6                  |              |                      |
| Fine HA         | National Cancer Institute | 4              | 2            |                      |
| Hjelmeland AB   | Duke University         | 4                  |              |                      |
| Ligon KL        | Harvard University      | 4                  | 2            |                      |
| Bao SD          | Duke University         | 3                  | 3            | 1                    |
| Bigner DD       | Duke University         | 3                  |              |                      |
| Black KL        | University of Iowa      | 3                  |              |                      |
| Brennan C       | Memorial Sloan-Kettering Cancer Center | 3 |              |                      |
| Depinho RA      | Harvard University      | 3                  | 2            |                      |
| Li ZZ           | Cleveland Clinic        | 3                  |              |                      |
| Louis DN        | Harvard University      | 3                  |              |                      |
| Rowitch DH      | Harvard University      | 3                  | 1            |                      |
| Sathornsumetee  | Duke University         | 3                  |              |                      |
| Wu QL           | Duke University         | 3                  |              |                      |
| Yu JS           | Maxine Dunitz Neurosurgical Institute | 3 | 3            |                      |

DISCUSSION

Based on bibliometric analysis and systematic review, the following comparisons of the results can be made from the articles indexed in Web of Science.

First, at the time of study there were 2,040 articles on glioma stem cells included in Web of Science, of which 63 articles were cited more than 100 times. The articles were published between 1992 and 2010, of which about 81% were published after 2004. This may be associated with the successful isolation of stem cells from 14 patients with different types of gliomas in 2003[9], which encourage the study of the gliomas to a new point. The other reason for this phenomenon is the inherent bias of the citation analysis[77]. The total number of citations of an article accumulates over time, which means that older publications would definitely receive more citations than new ones. The study was performed at the beginning of 2013, the articles published after 2010 has a short span of time to generate citation rates.

Second, the number of publications on the fundamental study of glioma stem cells was far greater than that of clinical studies. Articles regarding the identification of glioma stem cells were most popular for authors. Surface markers for stem cells gained increasing attention: CD133, ABCG2, nestin, musashi-1, MELK are all considered as surface markers for glioma stem cell identification. Currently, most scholars use CD133 as a surface marker for identifying glioma stem cells. In the top-cited article, Singh et al[9] found that CD133-positive cells could differentiate in culture into tumor cells that phenotypically resembled the tumor from the patient. However, Ogden et al[68] found that human gliomas consistently express A2B5 in a large percentage of cells. In contrast, CD133 expression was less abundant and less consistent, with several glioblastomas containing very few or no detectable CD133+ cells. These cells still have the capacity to form tumors after transplantation into nude rats (92%). Other studies showed that CD133+ cells also had the ability to clone and form tumors[34, 73].

Third, the authors and institutes in the USA have published and registered most of reports on the studies of rehabilitation and other treatments for glioma stem cells. Duke University and University of California, San Francisco were found to be the most productive institutions, followed by Harvard University, Memorial Sloan-Kettering Cancer Center, and the National Cancer Institute. The articles written by authors Rich JN, Mclendon RE, and Hjelmeland AB, from Duke University, were predominant in citations.

Finally, the journals focusing on cancer published the most articles on glioma stem cell studies.

Our review has limitations. First, we searched articles in the Web of Science with “glioma stem cell” or “glioma, stem cell” or “brain tumor stem cell” in the topic field, which may miss some citations related to our analysis, such as papers regarding “tumor initiating cells”. Another limitation is citation analysis has oriented or biased citing, including self-citation, in-house, or negative citation, which is also a problem that should not be ignored[78]. An important thing to be mentioned is that impact factor or citation analysis is not an index to evaluate the quality of scientific research, but rather a measure of recognition. That is, the number of citations of an article is not considered equivalent to its importance[78].

CONCLUSION

Our bibliometric analysis provides a historical perspective on the progress in glioma stem cell research.
in the past 20 years. Papers originating from the outstanding institutions of United States and published in high-impact journals are most likely to be cited in the field of glioma research.

Author contributions: Fuxin Yi and Jun Ma designed and conducted the literature retrieval. Weimin Ni and Rui Chang assigned academic classification. Wenda Liu and Xiubin Han integrated the experimental data. Dongxiao Pan verified the data. Xingbo Liu and Jianwu Qiu supervised the study. All authors approved the final version of the paper.

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