

Research Article

Title: An evolutive and scientometric research on tissue engineering reviews.

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ABSTRACT

Publication numbers have been widely used as measure of research output, especially academic and university research. Publication numbers in tissue engineering (TE) have increased year by year since early 1990s. However, after an exponential growth phase, recently publications increase at lower rates, suggesting a consolidation process in which reviews become a relevant and high evidence document type. The aim of this study is to perform a scientometric evaluation of published literature reviews on TE in order to assess the status of scientific evolution and confirm the consolidation of TE as a research area. Published reviews on TE from 1991 to 2018 were retrieved from Web of Science core collection and this corpus of knowledge was analyzed by growth rate, research area, source title and citation. Our results revealed that TE can be considered a consolidating area as it leaves the forefront stage of a gompertzian growth curve model. Original research/review ratio is lineally decreasing during the last decade. The emergence of reviews serves to confirm and refute hypothesis and build up a more reliable theoretical framework as well as a guide for future educational approaches. Distribution assessment of categories and journals indicates the multidisciplinary profile of this area focused on the design and development of new tissues. Biomedical sciences become relevant productors of reviews to as they need to support TE innovations with

high evidence leading to a safer and more efficient treatment of current injuries and diseases.

IMPACT STATEMENT

Scientometric analysis of published reviews about tissue engineering suggests that can be considered a consolidating area as it leaves the forefront stage of a gompertzian growth curve model. Biomedical sciences become relevant producers of reviews as they need to support TE innovations with high evidence leading to a safer and more efficient treatment of current injuries and diseases.

Keywords: Tissue engineering, literature reviews, scientometrics, evolution, advanced therapies.

INTRODUCTION

The output of information in science is overwhelming. In 1961 Derek J. de Solla Price published the first quantitative data about the growth of science from 1650 to 1950. His data showed an exponential growth rate of publication, increasing about 5.6% per year and a doubling time of 13 years. The number of articles recorded for 1950 was about 60,000 and the forecast for year 2000 was about 1,000,000 ¹. Recent research studying science output up to 2012 have identified different stages of growth in terms of published documents and cited references ². After the First World War, and as a consequence of economic growth, science started to increase at 8% each year, doubling every 9 years, revealing an overgrowth stage followed by a decrease in the rate of publication and the consolidation of research.

Publication numbers have been used as measures of the output of research, especially academic research and university research. Analysis of publication numbers are based on big databases for scientific publications. Some of the databases also give the basis for measurements of citation, which are usually used as indicators of the quality of publications ³.

Specifically, recent reports are trying to characterize tissue engineering as a consolidating research field through scientometric analyses on the corpus of literature ^{4,5}. Tissue engineering (TE) is an area of research aimed to the development of artificial tissues and organs that could restore maintain or even improve anatomical and/or functional integrity of injured tissues ⁶. From early 90s, it has been reported that publication numbers in TE have increased year by year. However, after an exponential growth phase, recent years publications increase at lower rates, suggesting a consolidation process ⁵.

Even, the literature reviews play a key role in consolidation of obtained knowledge ⁷. Reviews are in great demand and their need stems from that ever-increasing output of scientific publications ^{8,9}. Literature reviews provide a much-needed bridge between the vast and scattered amount of articles on a topic and the reader who does not have time or resources to track them down. Even, there is a wide heterogeneity in the quality of published information and its impact. Good science influences the direction of science itself, and the development of new technologies and social policies. Poor science leads to dead ends, either because it fails to advance understanding in useful ways or because it contains important errors. Poor science produces papers that can eventually feed the fireplace, or in a more modern and ecologically friendly version, the accumulation of electronic documents ¹⁰. Reviews show the capability to discriminate between good and poor science, emerging conclusions of a scope and theoretical level that experimental reports cannot normally address ¹¹. In addition, its role in educational activities is relevant as a source of selected, updated and rigorous knowledge to be transmitted in the different educational levels through appropriate didactic approaches. Consequently, literature reviews may play a key role in the synthesis, the construction of theories and learning in research areas that have gathered a large amount of empirical information.

The aim of the present work is the scientometric research of published literature reviews on TE from 1991 to 2018 in order to assess the status of scientific evolution and confirm the consolidation of TE as a research area.

MATERIAL AND METHODS

Analyzed metadata used in this investigation were retrieved from the Clarivate Analytics Web of Science (WoS) core collection database of the Institute for Scientific Information (ISI) (Philadelphia, PA, USA). WoS is considered one of the most complete and reliable databases of scientific information, gathering information of 8,917 scientific journals.

Documents were retrieved by searching (“TISSUE ENGINEER*” or “TISSUE-ENGINEER*”) as topic on SCI-Expanded collection as previously described ⁵, from 1991 to 2018. Obtained results were filtered by publication type and only reviews were refined excluding other publications.

All the reviews referring to TE in the past 28 years (from 1991 to 2018) were assessed by growth rate, WoS research areas and categories, source title and citation count. Leading to a further comprehension of global trends, some of these analyses were performed over 3 time groups: (1) from 1991 to 1999, (2) from 2000 to 2008 and (3) from 2009 to 2018. The selection of these ranges were adjusted to global production taking into account that the amount of documents is higher as time goes nearer to nowadays.

RESULTS

Growth rate of publication

7,084 published reviews were retrieved from ISI Web of Science after performing the search strategy previously described, ranging 28 years of global production that form the corpus of review literature at TE. From 1991 to 1999, 55 reviews (0.78% of total

production) were reported. This growth rate of production starts increasing from 2000 to 2008 with the publication of 1248 reviews (17.62%) and mainly during the last decade, from 2009 to 2018, when 5781 reviews on TE (81.61%) were retrieved.

The rate of review publication can be closely adjusted to a third degree polynomic model $y = 0.584x^3 - 8.874x^2 + 44.378x - 56.523$ ($R^2 = 0.999$) that can be used to predict the report of new reviews in the near future. In this sense, the publication rate will probably keep increasing during the last decade and it can be estimated that the total amount of reviews will be higher than three- fold current production in 2029.

The growth rate of publication of original research can also be correlated to a polynomic model ($y = 2.194x^3 - 4.331x^2 - 171.21x + 546.3$; $R^2 = 0.999$), as reviews do. However, these two document types are not increasing at the same rate. In fact, ratio original research/review has been lineally decreasing from 1991 to 2018 ($y = -0.099x + 8.551$; $R^2 = 0.905$), mainly during the last evaluated subperiod, from 2009 to 2018 (Figure 1)

Research areas

Retrieved documents show a highly heterogeneous pattern of distribution among Web of Science research areas. A total of 131 scientific research areas (excluding Arts & Humanities and Social Sciences) are implied in the corpus of TE reviews.

The most productive research areas were “Biotechnology & Applied Microbiology” (8.11%), “Engineering Biomedical” (7.87%), “Cell and Tissue Engineering” (7.07%), “Cell Biology” (6.94%) and “Material Science Biomaterials” (6.80%). As can be seen in Figure 2, the production of reviews from 1991 to 1999 is very low probably due to the absence of data during the first decade of TE development as a scientific discipline.

The growth of these research areas has been increasing from 2004 to nowadays with similar rates. When taken together, these five research areas gathers 36.79% of the total number of reviews and each one presents relative weights that are very similar, mainly since 2007 to nowadays (Figure 3).

Source title

The publication of TE reviews presents a wide range in terms of source titles and up to 1451 different journals have reported at least one of the 7084 retrieved documents. Nevertheless, the distribution of reviews in this journals is not homogeneous as 83.18% (1207 journals) have reported 5 or less reviews at the same time as 1.03% (15 journals) are implied in the publication of 20% total reviews.

The Bradford's journals core, a set of journals publishing 25% of total amount of documents in a scientific discipline, has been increasing from the first decade (3 journals), through the second subperiod, when the Bradford's core was composed by 10 journals and finally, from 2009 to 2018 up to 20 journals (Table 1). *Advanced Drug Delivery Reviews*, *Tissue Engineering Part B Reviews*, *Biomaterials* and *Acta Biomaterialia* are considered the most productive sources with more than 100 documents each of them and gathering almost 10% of the whole corpus.

Citation analysis

Total citation count was obtained from WoS as an index of the global impact of TE reviews. The average citation resulted in 62.69 citing articles per document. Analyzed Hirsch-index was obtained to be 286. 1780 of 7084 total reviews (25.12%) obtained less than 5 cites. However, more than half (52.65%) of all the retrieved reviews were published during the last 5 years, which suggest that a significant amount of reviews have not yet reached their real impact in terms of citation as they collect 15.83% of total

citation. Most relevant reviews, documents with highest citation, could be identified. 6.59% reviews collected more than 100 cites, 1.95% of total documents achieved more than 500 cites and there are up to 39 reviews (0.55%) gathering more than 1000 cites, which could be considered as keystone papers. The 10 most cited reviews and its citation are shown in Table 3. All these keystone reviews presents more than 2000 cites each one. Even when taken together these 10 documents (0.14% total reviews), they accumulate 25530 cites (5.74% total citation). These top cited reviews are not recent as its year of publication ranges from 2001 to 2010, suggesting that it is not possible to estimate real impact of an important extract of the corpus of TE reviews.

9 of these 10 top cited reviews are focused on the importance of biomaterials research, hydrogels and polymeric biomaterials with suitable use as cell scaffolds, suggesting this is one of the major challenges faced by TE as a scientific discipline.

DISCUSSION

The notion of tissue engineering first appeared in 1988 as an alternative clinical approach when transplantation of living tissues has failed ¹². During the last 30 years, tissue engineering has developed becoming a consolidating research field with a corpus of literature composed by more than 34,000 high-impact published scientific documents ⁵.

The scientometric study of the production of tissue engineering is interesting and necessary as it allows arising the evolution patterns of that field of knowledge. Even, as Freedman stated, science is a human activity focused not only in the obtention of increasingly fuller and more accurate knowledge of nature. Science is also related with an increasing potential to adapt itself and change its environment ¹³. In this sense, tissue

engineering as a research field could be the base of translational research leading to new therapeutical approaches that may improve current treatments and quality of life.

Thus, the main objective of this study was the description of the global trends around tissue engineering reported reviews. Literature reviews provides a much-needed bridge between the vast and scattered assortment of reported articles and the reader who has no time or resources to track them down, as indicated previously. Also, research reviewing is a valuable theory-building technique that is not only important to know what knowledge should be transmitted in education, but also to generate hypothesis for further development of the field of knowledge ¹¹. These are some of the reasons for literature review to be considered as high scientific evidence documents in science.

Scientific fields are not static entities. They dynamically change during the evolution of science ¹⁴. These changes and evolution are driven by the development of related disciplines, the emergence of new technology and socioeconomic factors and are directed to solve consequential problems in nature and society ¹⁵. Scientometrics provides tools to assess the evolution of research fields, as well as its cognitive and social framework ⁴. In this sense, more than 80% of total 7,084 reviews reported in TE research for almost 30 years have been published during the last decade, suggesting that the growth rate of publications increases as TE demands synthesis and development of theoretical framework over collected knowledge. Also, our results showed that the proportion between the production of original research and reviews is lineally decreasing mainly from 2009 to 2018. A relative growth of reviews in comparison to original research is a typical feature of scientific disciplines that are leaving a stage of exponential growth and becoming consolidating areas, when the main need is not the collection of data but the application of strategies that limit bias in the assembly, critical appraisal and synthesis of relevant studies ¹⁶. These results accord with previous reports

by our group analyzing the global production of TE original research and concluding that the evolution of TE might be on a transition between the forefront and consolidation stages as it has followed an exponential model until 2011. From 2011 to the present the growth rate is under the exponential model ⁵. Our previous findings together with the results obtained in the present study regarding literature reviews confirm that TE is not an emerging area but a consolidating discipline.

The characterization of the corpus of review literature in TE also revealed that this need of synthesis is widely transversal, as more than 130 scientific research areas have participated, confirming the multidisciplinary profile inherent to Advanced Therapies. The WoS research areas are based on citation rates of different sets of journals and it could lead to overlapping among disciplines due to assignment of one journal to one or more categories ¹⁷. Nevertheless, WoS subject categories have been used in this study due to the broader range of covered scientific disciplines. Furthermore, it has become a well-established practice in evaluative bibliometrics ¹⁸.

However, not all the disciplines showed the same relative contribution to TE. Instead, few categories are responsible of a significant fraction of the review production. Among the most productive research areas we can find either basic —*Materials Science Biomaterials* and *Cell Biology*— or applied sciences — *Cell & Tissue Engineering*, *Biomedical Engineering* and *Biotechnology & Applied Microbiology*. These findings are in accordance to obtained in other emergent research fields as human microbiome, robotics or astrobiology, where 80% of production was located in 3-5 research areas with a combined contribution of basic and applied fields ¹⁹. In the case of TE, these 5 categories are around 40% of total review production. This fact can be explained by the high occurrence of different disciplines needed for the development of artificial tissues and organs as well as TE is more long-lasting when compared to microbiome or

astrobiology. Even, these five research areas present very similar relative weights during the last decade. These results suggest a multidisciplinary contribution to synthesis and review of reported data.

Analyzed results also tended to confirm some of the major bibliometric rule as Bradford's journal distribution law that estimates the exponentially diminishing returns of searching for references in science journals²⁰. In fact, 5 journals collect up to 10% of all reported reviews. It is interesting how the Bradford's core of journals publishing the 25% of the corpus has increased during the last decade. This finding could be explained through the profile of currently available journals. There are not enough specialized review-scoped journals that could gather most of documents. Instead, there a few journals devoted to review publishing and have become the most productive, as well as journals aimed to report several document types. This is a good example on how bibliometric analysis could serve to evaluate the current status of a research field and the probable evolution in near future. Probably, new journals dedicated to the outreach of reviews will emerge during next years as a solution to the need of synthesize all collected data and conform a more reliable theoretical framework around TE specially in tis medical applications, suggesting the definitive consolidation of tissue engineering as a scientific discipline. This is going to be more important in the future of TE as advanced therapy because this new therapeutical tool need to be learned by medical students and residents of the different specialties, including primary care physicians²¹.

It is interesting that most of reviews are focused on biomaterials to be used as scaffolds and its relation with cells. Biodegradable scaffolds and, specifically hydrogels have been recently identified by science mapping analysis as one of the three main vectors promoting TE evolution from its beginning to nowadays⁴. Even, three of the ten most cited reviews are directly focused to the use of hydrogels in tissue engineering and

biomedical applications ²²⁻²⁴. Materials science is considered a keystone in TE development and new technology looks for new biomaterials with the optimal properties to be used as cellular scaffolds. Strikingly, journals belonging to WoS categories of Life Sciences & Biomedicine dominate over Technology or Physical Sciences categories in publishing TE reviews. Although there is a great effort of research in materials sciences, life sciences act as pivoting and central disciplines as the final aim of TE is the development of biological substitutes in order to restore, maintain or even improve tissue function ⁶. Thus, biomedical journals try to extract feasible conclusions of which biomaterials fit better with viable cells for an optimal functionality of artificial tissues and organs and, thus, a proper biointegration and clinical effectiveness.

Citation is oftenly used as an estimator of the impact of scientific documents ²⁵. It is not surprising that average citation of reviews and other synthesis documents is higher — even duplicating— when compared to original research articles ⁵, as reviews act as high-evidence documents, limit bias, constitute a guide for future learning of the discipline and even make up new hypothesis to be tested and confirm or deny previous ones. However, using citation as a marker of the impact of reviews in TE present some limitations. More than half of all retrieved reviews have been published during the last 5 years, so it is not yet reliable to measure the impact of the corpus through classical citation. In fact, 85% of obtained cites refers to documents published before 2014. In this sense, it would be very useful to use another impact measures to complement this information. Alternative metrics (altmetrics), based not on document citation but in social interactions, provide impact of scientific documents with more immediacy than classical metrics do ²⁶. Further characterization of the TE corpus of literature should be

performed by using altmetrics that may assess not only the impact of TE in scientific community but also in general society ²⁷.

Moreover, the use of the WoS database to perform the analysis could suppose a partial overview of the TE production is being assessed. In that way, Google Scholar is considered as a database that covers a broader range of records ²⁸. Nevertheless, it has been criticized for not ban the predatory journals ^{29,30}, does not have an adequate process of quality control ³¹ and to include a high rate of duplicates. These issues could compromise the reliability of our study, so WoS was used since it has been stated that this database is considered as a primary criterion in tenure, promotion and other professional decisions ^{32,33}.

In summary, the bibliometric characterization of all reviews documents in TE revealed that TE can be considered a consolidating and not an emerging area as it leaves the forefront stage of a gompertzian growth curve model. During the last years TE is gathering and synthesizing collected data for the last three decades in order to confirm and refute hypothesis and build up a more reliable theoretical framework and probably this trend will be more noticeable in near future. Distribution assessment of categories, and journals indicates the multidisciplinary profile of this area focused on the design and development of new tissues. Because these new tissues are mainly oriented to therapeutical purpose, biomedical sciences become relevant productors of reviews to support theses therapeutical innovations with high evidence leading to a safer and more efficient treatment of current injuries and diseases.

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COMPETING INTERESTS

All authors declare there is not any financial or personal relationship with organizations that could potentially be perceived as influencing the described research.

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