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Visualization analysis of research frontiers and trends in nerve regeneration and osseoperception in the repair of tooth loss

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Abstract

This study analyzed 85 articles indexed by the Web of Science concerning nerve regeneration and osseoperception during tooth loss repair. Using the Web of Science database and Citespace III software, a document co-citation network map was drawn by document co-citation analysis and word frequency analysis methods. Combined with emergent node secondary literature retrieval, subject headings with apparent changing word frequency trends were retrieved so as to identify research frontiers and development trends. Research frontiers and hotspots for neuronal calcium sensor protein were quantitatively explored to forecast future research developments in nerve regeneration and osseoperception during repair of tooth loss.

Key Words: *nerve regeneration; tooth nerve injury; peripheral nerve injury; nerve repair; osseoperception; neuroprotection; scientific map; Web of Science; Citespace; neural regeneration*

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Introduction

Tooth nerves mainly arise from the maxillary and mandibular branches of the trigeminal nerve, and sensory nerve fibers enter the pulp cavity along with the apical foramen. Thick nerve fibers are visible in the central district, but gradually separate into small branches towards the dental crown and surrounding areas. Pulp sensory nerve endings are free nerve endings and nociceptors. Terminals that can play a role in mechanical irritation of the periodontal ligament are derived from myelinated nerve fibers. Clinical studies have verified that chewing and other oral functions are not obviously uncomfortable in most patients after repair of tooth loss, suggesting that dental implants and their oral and maxillofacial tissues form structural and functional integration. The proprioceptive sense, derived from the implant and the surrounding tissue, integrated by the peripheral nervous system and central nervous system, and similar to natural tooth sense, is called osseoperception (Abarca et al., 2006).

Osseoperception is an implant-related mechanical perception, which is derived from mechanical stimulation, and is transmitted by mechanoreceptors in the muscles, joints, mucous membranes, skin and periosteum tissue. It can cause sensorimotor function changes in the central nervous system (Klineberg et al., 2005). Nerve regeneration after tooth extraction or dental injury involves regeneration of sensory axons, regeneration of nerve endings and periodontal ligament reconstruction. During the above processes, the expression of many biologically active substances changes significantly. Mackenzie and Tonetti (1995) demonstrated that peri-implant epithelium and junctional epithelium had immunohistochemical characteristics similar to those of natural teeth, which indicated that peri-implant epithelium may also have a rich innervation. A previous study showed that a large number of nerve fibers were detected in the periodontal ligament of central incisors and canines of dogs after 4 months of healing (Sato et al., 1992). Wang et al. (1998) reported that the number of nerve fibers on the surface of implants increased with time. Weiner et al. (2004) verified that weight-bearing dog mandibular implants could stimulate inferior alveolar nerve action potentials. The effects of nerves on bone tissue include neurotrophic effects, regulation of blood flow changes, conduction of sensation changes, including pain, pressure and position variation. After tooth implantation, nerve fibers began to regenerate with the healing of soft and hard tissues and the formation of epithelial tissue surrounding the implant (Fujii et al., 2003). Simultaneously, nerve fibers that are rich in p-glycoprotein and calcitonin gene-related peptide emerge and gradually become

Table 1 Seven important articles analyzed by Citespace software

Rank	Citation counts	Centrality	Cited literature	Half-life
1	158	0.79	Nkenke et al. (2001)	1
2	60	0.34	Nkenke et al. (2002)	3
3	55	0.06	Thomadakis et al. (1999)	2
4	50	0.14	Raghoebar et al. (2001)	3
5	50	0.02	Maeda et al. (1999)	1
6	48	0.55	Robinson et al. (2004)	2
7	42	0	Misch (1997)	8

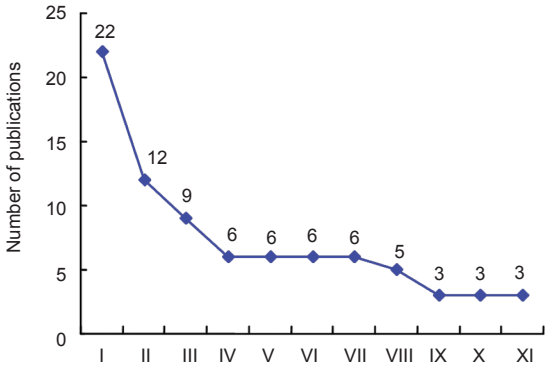

Figure 4 The countries from which more than two publications were published on osseoperception and nerve regeneration in the repair of tooth loss indexed by the Web of Science.
I: USA; II: Japan; III: Belgium; IV: Switxerland; V: Sweden; VI: Germany; VII: Brazil; VIII: China; IX: South Korea; X: Norway; XI: France.

densely distributed in soft tissue surrounding the implant. In addition, large numbers of neurofilament protein-stained fibers surround the implant. These fibers are distant from the wall of periodontal blood vessel and are unlikely to be derived from the intraosseous nerve, which has a vasoconstrictor function. The above fibers might be regenerating nerves that surrounded the natural tooth. Studies addressing osseoperception of dental implants have mainly focused on morphological observation surrounding the implant, electrophysiological assessment and advanced cortical functional integration. After tooth nerve damage, the questions of how to repair and regenerate tooth nerves, elevate peripheral nerve regeneration levels, and elevate the degree of osseoperception of the implant so as to be close to the level of the natural tooth are important issues in basic and clinical researches.

CiteSpaceIII is a free Java application created by from Drexel University that users can download to visualize and analyze trends in scientific literature (Chen, 2006, 2009). CiteSpaceIII can be used to explore the dynamics of scientific frontiers and knowledge on the dual basis of time variables between scientific frontiers and knowledge (Chen, 2006).

Knowledge mapping tools for analyzing research and development trends of specific areas have been a major research focus in information science of academic and professional fields in recent years (Chen, 2006, 2009). We have found that studies published outside China have utilized Citespace visualization bibliometric analysis tools to investigate knowledge structure. They have found unexpected trends and key turning points in the fields of regenerative medicine, cloud computing, neurological sciences, education

Table 3 The agencies that published more than two Web of Science-indexed articles concerning osseoperception and nerve regeneration in the repair of tooth loss

Agency	Country	Number	% of total number
University of Leuven	Belgium	9	10.59
University of California System	USA	8	9.41
Universidade De Sao Paulo	Brazil	5	5.88
Karolinska Institutet	Sweden	5	5.88
University of Bern	Switzerland	4	4.71
Niigata University	Japan	4	4.71
Harvard University	USA	4	4.71
University of Bonn	Germany	3	3.53
University of Bergen	Norway	3	3.53
Osaka University	Japan	3	3.53

research, nano-bio-medicine, heat integration, knowledge management, public information resources management and artificial intelligence, and to discover knowledge bases, research focus, research frontiers and trends of the corresponding disciplines. However, visualization tools have not been used to analyze knowledge mapping or research frontiers concerning nerve regeneration and osseoperception during tooth loss repair.

Research Methods and Data Sources

We retrieved articles or reviews from the Web of Science (http://apps.webofknowledge.com). The subject headings, in English, were osseoperception or (periodontal Ruffini endings AND regeneration) or (inferior alveolar nerve AND regeneration). A total of 85 original articles or reviews were retrieved. The date of retrieval was October 8th, 2014.

Inclusion criteria

(1) Published, peer reviewed, original articles (basic research and clinical research) and reviews on osseoperception and nerve regeneration during tooth loss repair; (2) retrieved from the Web of Science; (3) full-text articles.

Exclusion criteria

(1) Articles that have to be retrieved by hand and telephone; (2) unpublished articles; (3) conference abstracts and conference proceedings, corrigendum documents; (4) repeated publication; (5) unrelated articles were excluded.

All 85 documents were downloaded, including authors, title, abstract, descriptors and identifiers. The number of references was 917. The downloaded data were inputted into CitespaceIII software for visual pattern analysis. Finally, 14,778 valid data were obtained.

Results

Studies concerning osseoperception and nerve regeneration during the repair of tooth loss indexed by the Web of Science

CitespaceIII software was applied to visually analyze the

Table 2 Seven largest clusters among co-cited publications marked by subject headings

Cluster ID	Size	Silhouette	Mean (cited year)	Top terms (term frequency-inverse document frequency weighting)	Top terms (log-likelihood ratio)	Terms (mutual information)
8	92	0.913	1989	Expanded (18.01); polytetrafluoroethylene (18.01); entubulation (16.55); conduit (12.85); vein (11.8)	Vein (140.22); expanded (134.04); polytetrafluoroethylene (134.04); nerve (110.26); entubulation (93.65)	Partial
22	64	0.972	1993	Ruffini (21.97); endings (19.38); processes (18.86); cytochemical (18.86); characteristics (18.86)	Periodontal (396.36); Ruffini (291.15); incisor (159.36); endings (153.93); regeneration (137.82)	Basis
6	39	0.91	1996	Intraoperative (9.87); lateralization (8.75); rabbits (8.59); oryctolagus (8.59); cuniculus (8.59)	Diagnosis (34.38); intraoperative (28.43); etiology (26.46); implant (25.74) neurosensory (24.8)	Advanced
7	31	0.929	1995	Microsurgical (12.2); retraction (10.68); flap (10.68); lingual (10.19); third (9.12)	Lingual (77.32); microsurgical (74.28); repair (59.07); review (41.67); injuries (36.65)	Pharmacologic
15	28	0.914	1993	Topical (12.05); modulation (12.05); implications (9.87); mechanisms (7.54); input (7.54)	Topical (47.84); modulation (47.84); input (47.84); implications (38.44); mechanisms (35.82)	Partial
14	28	0.984	1997	Soft (8.69); magnetic (8.59); tactile (8.16); tissues (7.75); sensibility (7.53)	Tactile (61.52); oral (46.43); soft (45.22); osseoperception (43.82); tissues (42.86)	Findings
19	25	0.899	2001	Sensorimotor (15.27); movements (14.89); neuroplasticity (14.27); cortex (14.27); motor (14.17)	Sensorimotor (188.4); neuroplasticity (142.44); face (142.44); cortex (142.44); orofacial (102.16)	Getting

Table 4 The eight articles with the highest citation frequency indexed by the Web of Science

No.	Title	First author	Journal	Publication year	Total citations
1	Morbidity of harvesting of chin grafts: a prospective study	Nkenke E	*Clinical Oral Implants Research*	2001	158
2	Immunolocalization of bone morphogenetic protein-2 and-3 and osteogenic protein-1 during murine tooth root morphogenesis and in other craniofacial structures	Thomadakis G	*European Journal of Oral Sciences*	1999	55
3	The Ruffini ending as the primary mechanoreceptor in the periodontal ligament: Its morphology, cytochemical features, regeneration, and development	Maeda T	*Critical Reviews in Oral Biology & Medicine*	1999	51
4	Current management of damage to the inferior alveolar and lingual nerves as a result of removal of third molars	Robinson PP	*British Journal of Oral & Maxillofacial Surgery*	2004	47
5	Gore-Tex tubing as a conduit for repair of lingual and inferior alveolar nerve continuity defects: A preliminary report	Pogrel MA	*Journal of Oral and Maxillofacial Surgery*	1998	38
6	Mechanisms of oral somatosensory and motor functions and their clinical correlates	Sessle BJ	*Journal of Oral Rehabilitation*	2006	37
7	The use of autogenous vein grafts for inferior alveolar and lingual nerve reconstruction	Pogrel MA	*Journal of Oral and Maxillofacial Surgery*	2001	36
8	Low-level laser effect on neural regeneration in Gore-Tex tubes	Miloro M	*Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontics*	2002	33

articles addressing osseoperception and nerve regeneration during tooth loss repair. Time Slicing was set to 1. Data published from 2000 to 2014 were assigned to 15 time periods. The first 50 articles with the highest citation frequency were selected in each period. Node type was burst terms. Pathfinder network scaling was selected for network simplification. The co-citation-emergent term visual analysis network knowledge map is displayed in **Figure 1** and contains 572 nodes and 1,683 lines.

The research frontier of a particular area is embodied by active citations by scientists, and represents the ideological situation of a field. The articles with high citation frequency show the core results in that field. Nevertheless, citation frequency is not directly correlated with the contribution of the articles to the study process. The status and contribution of the articles in the study process are embodied by variation value. New trends in the scientific literature and appearance of emergence may be guided by (1) new scientific

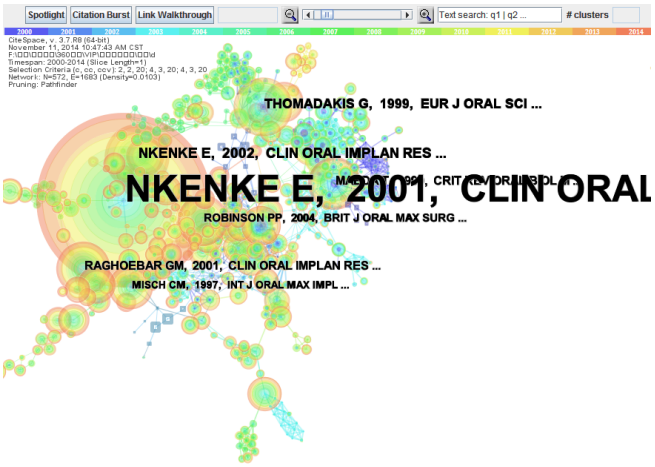

Figure 1 Co-citation-emergent term visual analysis network knowledge map.

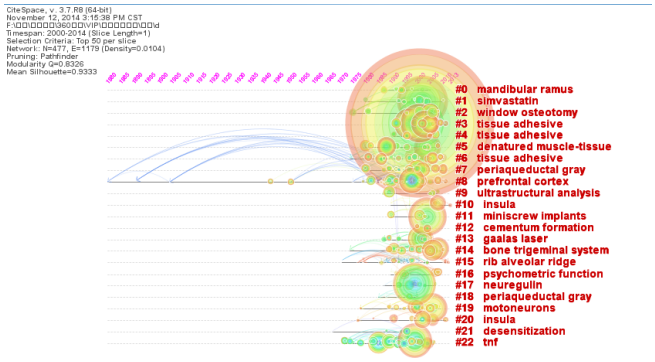

Figure 3 High frequency words addressing osseoperception and nerve regeneration in the repair of tooth loss in each period.

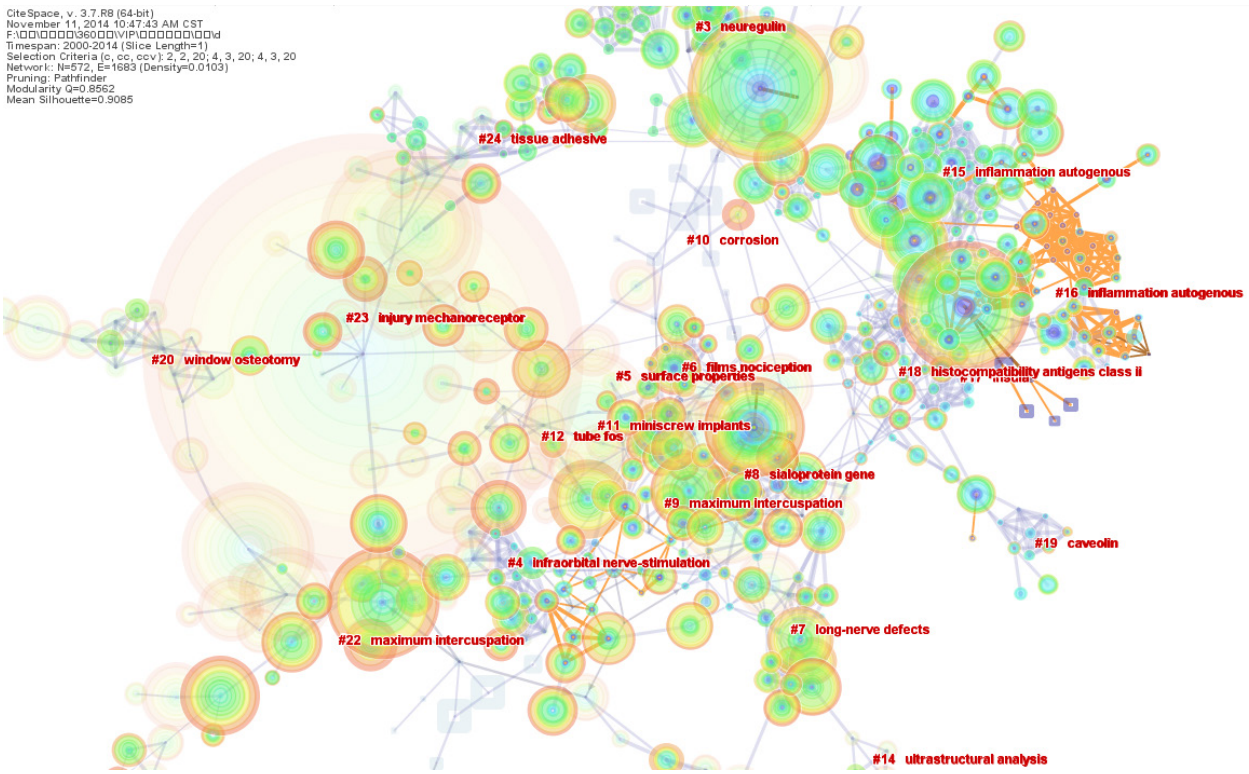

Figure 2 Co-word visual network map of studies concerning osseoperception and nerve regeneration in the repair of tooth loss.

discoveries and breakthroughs proposed by a publication; (2) publications may inspire scientists to study a problem from a new angle (Chen, 2004). On the basis of analyzing the document co-citation network map, publications with high citation frequency were retrieved twice so as to seek for and analyze research frontiers for nerve regeneration and osseoperception in the repair of tooth loss. Seven publications with high citation frequency were at the core of the cluster, and the core of the entire co-citation network. Each of them presents a new discovery, is the starting point of a line of study, represents a new trend, and leads a research direction (**Table 1**).

Co-citation clusters consist of articles that, due to co-citation, gather and form a network. These clusters represent new frontiers of research. Visualization results revealed that the co-citation cluster of publications addressing nerve regeneration and osseoperception during the repair of tooth loss formed an elliptical network, and all surrounding clusters were relatively independent. The cluster network, with the publication of Nkenke et al. (2001) as a center, intertwined, and was tightly connected. Modularity Q was 0.8562, and the average silhouette degree was 0.9085. The above data demonstrated that co-cited publications formed a sharp and relatively independent cluster network, and label description

of each cluster was relatively accurate, which provided reliable evidence for data analysis.

Co-cited publications formed 46 co-citation clusters, which were numbered 0–45 according to the number of references in each cluster network. This study analyzed the seven largest clusters (**Table 2**). Consistent with the labeled word in document co-citation clusters, scholars used different repair and treatment methods for nerve injury and investigated functional recovery after repair. We found that the highly cited articles on nerve regeneration and osseoperception in the repair of tooth loss mainly involved morphological observation. These studies laterally and deeply explored tissue engineering materials, and reflected the research frontier of nerve regeneration and osseoperception in tooth repair.

Visualization analysis of study hotspots concerning osseoperception and nerve regeneration in the repair of tooth loss

The pathfinder algorithm was used, taking the network node as the key word, node type: noun phrases, timezone: 1 year, and threshold for citation, cocitation, cosinecoefficient (2, 2, 20), (3, 3, 20), (3, 3, 20). A co-word visual network map was drawn (**Figure 2**). Figure 2 contains 572 nodes and 1,683 lines.

To more clearly understand the research focus of each time period, timezone view was used to analyze study hotspots marked by key words and to grasp the overall development trend of a discipline or research topic. According to citation counts and centrality, the hotspot in each stage was selected. Combined with the citation counts and centrality of key words, we found that hot-words mainly concerned repair methods of tissue engineering and inflammation control (**Figure 3**).

Spatial distribution of Web of Science-indexed studies concerning osseoperception and nerve regeneration during the repair of tooth loss

There were 98 articles concerning osseoperception and nerve regeneration during the repair of tooth loss, including 85 original articles and reviews. Publication year centered around 2000. The number of articles increased gradually over time.

The countries in which studies were performed are exhibited in **Figure 4.**

The greatest number of articles on osseoperception and nerve regeneration in the repair of tooth loss indexed by SCI was from the USA (22 articles), followed by Japan (12 articles) and Belgium (9 articles). The number from China (including Taiwan Region) was five.

Institutions publishing Web of Science-indexed articles concerning osseoperception and nerve regeneration during the repair of tooth loss are listed in **Table 3**.

The greatest number of articles (nine articles) from any institution originated from the University of Leuven in Belgium, followed by the University of California, USA (eight articles) and Universidade De Sao Paulo in Brazil (five articles) and Karolinska Institutet in Sweden (five articles). No Chinese agency produced more than two articles.

The eight articles with the highest citation frequency indexed by Web of Science are shown in **Table 4**.

Publishing of academic articles is an important metric that reflects research results. Citation frequency is extensively applied to assess the effect of a researcher or publication in a field. The citation frequency is significant to authors, journals and institutions (Adam, 2002). High citation frequency means that the research outcomes have been effectively disseminated and recognized by readers in a certain field. The number of citations has obvious shortcomings in the assessment of quality, but it is still widely considered to be the best method to judge the pros and cons of a journal or article (Nason et al., 2013). Citation has also been used to find "classic publications" (Moed, 2009; Rosenberg et al., 2010).

Discussion

The information visualization tool was used to draw a co-citation-emergence term visual analysis network knowledge map of nerve regeneration and osseoperception in the repair of tooth loss. Seven classic publications were obtained. Word-frequency analysis was employed to identify repair factors, such as neuropeptide Y, growth-associated protein-43, calcium binding proteins and various neurotrophic factor receptors. The detection of subject headings with significant word-frequency trends demonstrated that studies involving combinations of cells, such as Schwann cells, bone marrow mesenchymal stem cells, neural stem cells and pluripotent stem cells with tissue engineering scaffolds will be at the frontier in the field of nerve regeneration and osseoperception following tooth loss repair.

Bibliometrics and visualization analysis suggested that articles written by authors from academic institutions in the USA and those published after peer review in journals with high impact factors are most commonly cited.

A total of 85 articles on nerve regeneration and osseoperception in the repair of tooth loss were indexed by the Web of Science. The number of articles gradually increased with time. Most articles were published by institutions in the USA, Japan and Belgium. The number published in the USA and Japan accounted for approximately 50% of the total number. The strength of scientific research is equal between USA and Belgium in this field. The eight articles with the highest citation frequency were mainly published in 2000 or so. The article with the highest citation frequency was published in 2001, and was cited 158 times, on average 21.40 times per year. The number of articles with high citation frequency has reduced since 2006, which was probably associated with deviation of the citation analysis itself. The total citation count of an article accumulates over time. Compared with recently published articles, the citation count of articles published in the past will be high.

The 85 retrieved articles with high citation frequency were from 14 countries. Of them, most were from institutions in the USA (22 articles), indicating that the USA occupies a leading position in the study of nerve regeneration and osseoperception in the repair of tooth loss. Japan ranks number

two. Most of the countries with more than two articles were Western, developed countries. The University of Leuven in Belgium published nine articles with high citation frequency, and was ranked number one, followed by the University of California, USA (eight articles). No Chinese agency published more than two articles.

Conclusion

Osseoperception of dental implants involves many adaptive changes, from the peripheral sensory nerve mechanoreceptors to the central nervous system, and sensory nerve regeneration plays an important role. Peripheral nerve regeneration involves axons, Ruffini's nerve endings and other receptors. The expression levels of a variety of biologically active substances change during nerve regeneration, such as neuropeptide Y, growth-associated protein-43, calcium binding proteins and various neurotrophic factor receptors. Recently, stem cell transplantation for promoting nerve regeneration has become a hot topic. Implantation of Schwann cells, neural stem cells and mesenchymal cells can contribute to nerve regeneration surrounding the implant. Guided tissue regeneration can be applied to reconstruct periodontal tissue. This technique implants periodontal ligament stem cells that express high levels of bone morphogenetic protein, and platelet-derived growth factor and has achieved some success. Nerve regeneration and tissue engineering has made significant progress in recent years. Therefore, some scholars have incorporated this progress into the study and clinical application of osseoperception. Mesenchymal stem cells can be induced to become Schwann cells or their precursor cells, which can promote nerve regeneration surrounding an implant after transplantation so as to reconstruct the sensory projection to the midbrain and cortex. The above findings will be helpful to further investigate the establishment, maintenance and enhancement of osseoperception.

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