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Review

Cementum regeneration using stem cells in the dog model: A systematic review

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ABSTRACT

Objective: Restoring lost tissues of the periodontium, such as cementum, is essential in reducing the risk of tooth loss due to periodontitis and/or severe root resorption. Stem cell therapy is a regenerative strategy in cementum regeneration. This systematic review aimed to analyze the effect of various stem cells and their transplantation method on cementum regeneration in the dog model.

Methods: Electronic databases were searched, in addition to performing hand searches and a gray literature search. Titles and abstracts were searched according to the inclusion criteria and full texts were selected to be included in this systematic review. Data was extracted from each article and risk of bias was assessed for individual studies.

Results: Most studies reported that the treatment using a variety of stem cells resulted in significantly greater cementum regeneration.

Conclusions: Because of variations in additional factors included in each study and varied risk of bias among those studies, the effect of each type of stem cell on cementum regeneration in dogs is difficult to clarify. Additional information needs to be obtained from each study in order to further analyze the individual effect of stem cells on cementum regeneration in dogs.

1. Introduction

The periodontium is comprised of gingiva, alveolar bone, periodontal ligament, and root cementum (Schroeder, 1986). The gingiva is a combination of epithelial and connective tissues and is the portion of the oral mucous membrane that surrounds the teeth and the alveolar bone (Schroeder, 1986). The alveolar bone is the part of the maxilla and mandible that forms and supports the sockets of the teeth (Schroeder, 1986). The periodontal ligament is a type of connective tissue that lies between the tooth root surface and the alveolar bone (Schroeder, 1986). Occupying this periodontal space, the periodontal ligament connects the root cementum to the alveolar bone. Finally, cementum is the mineralized connective tissue that covers the entire surface of the anatomical tooth roots (Schroeder, 1986). Cementum helps to provide anchorage for the periodontal ligament extending to the alveolar bone (Schroeder, 1986).

There are many conditions that can damage the periodontal tissues. Gingivitis is an inflammation of the gingiva in the absence of clinical attachment loss (The American Academy of Periodontology, 2000); however, periodontitis is inflammation where there is pathological detachment of collagen fibres from the cementum and the junctional epithelium has migrated apically (Savage, Eaton, Moles, & Needleman, 2009). Gingivitis can progress to periodontitis; the latter is irreversible and a major cause of tooth loss (Chapple et al., 2015).

Another condition involved in periodontal tissue damage is root resorption, which involves the destruction of cementum (Chen & Jin, 2010; Fuss, Tsesis, & Lin, 2003). The etiology of root resorption includes injury associated with the outer root surface, the precementum, the inner surface of the root canal, or the predentin (Fuss et al., 2003). Root resorption can be observed during ankylosis between the alveolar bone and the tooth root (Karring, Nyman, Lindhe, & Sirirat, 1984), and may be caused by mechanical stimulation like dental trauma, surgical procedures, and excessive pressure (Fuss et al., 2003). Another cause of injury resulting in root resorption include chemical irritation, such as bleaching procedures (Fuss et al., 2003).

Root resorption in permanent dentition has a pathologic basis (Karring et al., 1984). Precursor clastic cells become multinucleated and activated, and then begin the process of breaking down the dental cementum and forming resorption lacunae, which are small and large pits on the surface of the tooth root (Arana-Chavez & Bradaschia-Correa, 2009). After resorptive activity, repair may naturally occur if the damaged surface is not large (Fuss et al., 2003). The remodeling

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process begins through osteoblast activity. Osteoblasts are derived from mesenchymal stem cells. Repair of the resorption lacunae occurs by the osteoblasts migrating into these pits and synthesizing new un-mineralized bone matrix that fills the lacunae and becomes mineralized (Neve, Corrado, & Cantatore, 2011).

Periodontal tissues damaged by these conditions may be either repaired or regenerated. Regeneration is the reconstruction or reproduction of a lost or damaged part of the body so that the design and function of these tissues are completely re-established. When healing is achieved by repair only, the tissues heal without this complete restoration and other tissues may replace the damaged or lost ones (Bosshardt & Sculean, 2009). This may appear as scar tissue, or in periodontal repair as junctional epithelium where a tooth attachment apparatus was originally located and functioning (Bosshardt & Sculean, 2009). Whether these tissues heal by repair or by regeneration depends on the availability of the needed cell types and on the presence or absence of necessary cues and signals for recruitment and stimulation of cells (Grzesik & Narayanan, 2002). In the absence of stem or progenitor cells, adult tissues may heal by repair (Grzesik & Narayanan, 2002). However, it is now recognized that the cells needed for regeneration are present in most tissues (Grzesik & Narayanan, 2002). In periodontal regeneration, the aim is to regenerate and restore various periodontal components affected by disease to their original form, function, and consistency (Garrett, 1996). So far, therapeutic strategies aiming to regenerate the periodontium have shown partial success (Chen & Jin, 2010). Many of these regeneration therapies use dental materials or derivatives of dental materials to restore lost dental tissues, but because of the lack of clinically-efficient periodontal regenerative modalities, there has been an increase of research for additional regenerative strategies, including stem cell therapy (Chen & Jin, 2010).

Among the variety of dental materials used in periodontal regeneration, mineral trioxide aggregate (MTA) is suggested to be the most promising dental material for treating root resorption (Katsamakis, Slot, Van der Sluis, & Van der Weijden, 2013). MTA was originally applied in the root canal for root and furcal perforation repair and retrofilling of root-end cavity preparations; however, it has also been shown to induce bone regeneration and stimulate osteoblast differentiation (Marão et al., 2012). These findings may make MTA a possible option for cases of external root resorption. Other treatment options for root resorption, which include the application of porcine enamel matrix on denuded root surfaces in monkeys (Hammarström, Alatli, & Fong, 1996) and the clinical use of Emdogain (Chen & Jin, 2010), are believed to induce root cementum formation. Emdogain is a formulation of enamel matrix derivative (EMD) (Chen & Jin, 2010). EMD is comprised of proteins in the amelogenin family that are produced by the Hertwig epithelial root sheath (HERS) (Chen & Jin, 2010). These proteins play a role in cementogenesis and may be important in regeneration of periodontal tissues (Chen & Jin, 2010).

Stem cell therapy has recently achieved research focus for tissue regeneration. Stem cells are the foundation cells for every organ and tissue in the body, including the periodontium, and include two types: embryonic and adult stem cells. Embryonic stem cells are derived from blastocysts and are pluripotent; however, their use in clinical therapy is a relatively new endeavor and currently being challenged due to ethical concerns (Ni-Hung, Gronthos, & Bartold, 2009) and the rapid formation of teratomas upon embryonic stem cell transplantation *in vivo* (Blum & Benvenisty, 2008). These teratomas are referred to as teratocarcinomas when they contain a core of malignant undifferentiated cells (Blum & Benvenisty, 2008). Adult stem cells, also known as tissue-specific stem cells, are multipotent stem cells that are found in the majority of fetal and adult tissues, and their use in research and medical applications is less controversial because these cells can be harvested without destroying an embryo (Estrela, Alencar, Kitten, Vencio, & Gava, 2011). The most common source of these cells is the bone marrow, but other sources include adipose tissue and dental tissues (Demarco et al., 2011). Dental tissue-derived mesenchymal stem cells are most commonly obtained from dental pulp, periodontal ligaments, apical papilla and dental follicles (Nowwarote, Sawangmake, Pavasant, & Osathanon, 2015). These cells express mesenchymal stem cell markers and have multipotential differentiation ability (Nowwarote et al., 2015). The strategy of using these cells for regeneration is achieved by providing them with the appropriate spatial and temporal cues to enable growth, differentiation, and synthesis of a functional volume and integrity of extracellular matrix (Chen & Jin, 2010). These cues may be in the form of medical devices, matrix, growth factors (ie. fibroblast growth factor, transforming growth factor (Galler, D'Souza, & Hartgerink, 2010), bone morphogenetic proteins (Galler et al., 2010)), cell adhesion molecules (Galler et al., 2010), cell or tissue scaffolds, and tissue-engineered constructs (Chen & Jin, 2010). Adult stem cells have been shown to form cementum, periodontal ligament, and alveolar bone *in vivo* after implantation into periodontal defects in dogs (Demarco et al., 2011). Since these stem cells have the ability to differentiate into dental tissues, they are a promising source for use in periodontal regeneration (Ni-Hung et al., 2009). It has been suggested that regeneration of cementum is the gold standard in periodontal regeneration (Chen & Jin, 2010) because cementum is the site where attachment of new tissue needs to be re-established (Grzesik & Narayanan, 2002). It is also a source of many growth factors that influence the activities of various periodontal cell types (Grzesik & Narayanan, 2002).

Studies using different animals involving periodontal regeneration have been performed; however, dogs are the preferred animal model because they have a periodontal physiology reasonably close to human periodontium, have clinically relevant size and tooth configuration, and are significantly easier to handle during postoperative management (Lee, Stavropoulos, Susin, & Wikesjö, 2010). Additionally, periodontal disease naturally occurs in this canine model and mimics the pathophysiological mechanisms of human periodontal disease (Albuquerque et al., 2012). Other animal models, such as the rodent, may be used for these types of studies, but there are significant differences in dental anatomy, inflammatory processes, and periodontal lesions compared to humans (Albuquerque et al., 2012).

Many studies have explored the use of different types of stem cells in various components of periodontal regeneration, including cementum. Although there are systematic reviews that analyze the potential of using stem cell therapy in periodontal regeneration (Chen & Jin, 2010; Demarco et al., 2011; Lin, Gronthos, & Bartold, 2009; Silvério, Benatti, Casati, Sallum, & Nocíti, 2008; Volponi, Pang, & Sharpe, 2010), only three systematic reviews have focused exclusively on periodontal regeneration including cementum regeneration with stem cells. Monsarrat et al. (2014) analyzed the key elements for efficacy and safety of mesenchymal stem cells used in periodontal regeneration in human and animal studies and only included articles published up to 2013, Bright, Hynes, Gronthos, and Bartold (2015) reviewed preclinical animal (dog, rat, pig, and sheep) studies using only periodontal ligament stem cells for periodontal (bone, cementum, and connective tissue) regeneration, and finally, Tassi, Sergio, Misawa, and Villar (2017) included a variety of preclinical animal studies using various mesenchymal stem cells for periodontal regeneration, but their systematic review is only updated to May 2015 and their included articles are limited in number. This is because the authors have missed some articles that were published before May 2015 and articles published after May 2015 were not available at the time of their electronic database searches. Hence, a specific and up-to-date systematic review that assesses the use of stem cells of any origin and their method of transplantation for cementum regeneration in periodontal defects, such as furcation and infrabony defects, in the dog, a preferred and more appropriate animal model, is timely.

2. Methods

The PRISMA statement was followed as much as possible.

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