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Disease models for the functional restoration of the periodontium based on developmental biology

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The tooth-supporting structures, which are collectively known as the periodontium, are disrupted in periodontal diseases. This disruption could lead to tooth loss at an advanced state. Therefore, the prevention and management of periodontal diseases are necessary to ensure a good quality of life. Different animal models are used to mimic the human periodontal disease conditions and examine the loss of tissues surrounding the teeth. The efficacy of various therapeutic compounds for the healing and regeneration of the disrupted structures were also examined. However, few studies have used animal models to examine the role of signaling molecules during the process of healing and regeneration. Since the signaling molecules play vital roles during the developmental processes, their role in the healing and regeneration of the periodontium must be evaluated based on the knowledge of developmental biology. This review highlights the process of periodontium development together with the role of signaling molecules. Furthermore, the disease conditions disrupting the periodontium and their severe consequences are also discussed. The different disease models commonly used for evaluation of the therapeutics and signaling molecules in periodontal diseases have also been reviewed, suggesting future research with a developmental biology approach in order to regenerate the periodontium.

Keywords: Periodontium, Experimental model, Periodontitis, Gingivitis, Regeneration

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Development of periodontium

Morphogenesis of periodontium

Periodontium comprises of the surrounding tissues which invest and support the tooth[1]. These tooth supporting tissues include the four major components; the gingiva, alveolar bone, periodontal ligament (PDL) and the root cementum[2]. The development of most of these tissues are accomplished together with the tooth root formation and tooth eruption and are originated from the dental follicle (DF) derived from the neural crest cells (NCCs)[3]. During tooth morphogenesis, the concentrated mass of neural crest ectomesenchymal cells around the tooth bud epithelium form dental papilla at the inner region surrounded by the dental follicle at the periphery[4]. As the development of tooth progresses, following crown formation, root formation initiates where the proliferating cervical loop forms the bilayered Hertwig's epithelial root sheath (HERS) which undergo proliferation and migrate downward guiding formation of root[5]. The interactions modulated by signaling molecules between HERS and the dental follicle cells initiate periodontium development forming cementoblasts, fibroblasts and osteoblast[6,7,8]. The cementoblasts differentiate into root cementum, while the fibroblast develop into PDL and the osteoblast give rise to the alveolar bone at the adjacent side of jaw bone during development of periodontium[8]. Further, during process of the eruption of tooth the crown pushes upward into the overlying oral epithelium resulting in the fusion of reduced enamel epithelium and the oral epithelium forming the junctional epithelium which is in close contact with the tooth[3]. This junctional epithelium continues with the oral epithelium which further develops into gingiva closely surrounding the tooth[7].

signaling pathways involved in differentiation of periodontium

Spatiotemporal expression of signaling molecules from the major pathways *Tgfb/Bmp, Shh, Wnt* and *Fgf* which play important roles in early tooth morphogenesis are supposed to be involved in reiterative epithelial-mesenchymal interactions during the development of periodontium[9]. However, there are very few reports which elucidate the signaling interactions involved during differentiation of periodontium. The Wnt signaling was reported to be involved in the proliferation of the PDL cells[10]. Further, the study carried out in periodontal defect animal model revealed that activation of canonical Wnt signaling enhanced regeneration of the cementum and PDL; the same report also showed that in vitro cultivation of hPDLCs in presence of LiCl and Wnt3a in the medium resulted in increased expression of gene/protein related to bone/cementum[11]. Moreover, Osterix (Osx) an essential transcription factor for osteogenesis was reported to be involved in cementogenesis[12]. And the expression of Osx was observed to be increased with stabilization of β-catenin which enhanced the process of cementogenesis[13]. The recent report also revealed that stabilized β-catenin results in increased Wnt signaling in the periodontium which leads to the formation of voluminous cellular cementum and alveolar bone together with calcified PDL leading to ankylosis of tooth[14]. This report implicated that there must be precise regulation of Wnt signaling in the periodontium for proper tooth function. In addition to Wnt signaling, Tgfβs known to have crucial roles in hard tissue formation in mammals have been reported to be involved in cementum formation via regulation of Osx expression[15].thus supporting Osx as probable central key molecule during the process of cementoblast differentiation. Also, the transcriptional factors such as Scleraxis, Gli, Msx1, Msx2 and Runx2 have also been reported to play roles in the differentiation of the DF into cementoblasts followed by mineralization of the cementum[16,17]. Further, several in vivo studies revealed that Bmp2, Bmp4, Bmp6, Bmp7 and Bmp12 are involved in the induction of cementum, periodontal ligament and alveolar bone regeneration[18,19,20,21].Among group of FGFs, FGF2 was reported to be effective in periodontal regeneration[22,23]. Taken together all these previous reports revealed that different signaling molecules are involved in periodontal regeneration, yet the specific signaling molecules that play vital role in differentiation of cementoblast, fibroblast and osteoblast forming overall periodontium from the DF are still in the research processes and are expected to be unravelled in future.

Diseases and traumatic injury in the periodontium

Periodontal diseases

The infections in the tissues supporting the tooth are known as periodontal diseases. The most common type of periodontal diseases are the gingivitis and periodontitis.

Gingivitis

Gingivitis is the inflammation of the gums or gingiva which is often non-destructive, reversible characterised by redness, oedema and bleeding which initiates with the accumulation of microbial biofilm, a dental plaque on teeth[24,25]. Inadequate oral hygiene leads to dental plaque formation which results in the dysbiosis of the oral bacterial flora at the subgingival surface of the tooth[26]. This bacterial colonization initiates the local inflammation which triggers the immune system and the cytokines are released in response to inflammation resulting in gingivitis[27]. Therefore, preventing the formation of dental plaque is important factor for the control of gingivitis[28]. Failure to treat this gingivitis in time further enhances the inflammation which progresses throughout the periodontal tissues[29].

Periodontitis

Periodontitis, the most prevalent periodontal disease is an irreversible inflammatory condition which results in sequential degradation of periodontium[30]. Failure to treat gingival inflammation leads to the destruction of underlying tooth supporting tissues the periodontal ligament and the alveolar bone as sign of severe periodontitis which ultimately results in tooth exfoliation[31,32]. The reports indicate that periodontitis is the sixth most prevalent disease in the world which affects millions of population world-wide[33]. Periodontitis is often painful and treatment is time consuming. However, it is preventable and its treatment leads to improved quality of life and reduced rates of tooth loss. The primary prevention of periodontitis is the management of gingivitis while the important preventive measures need the behavioral changes to mitigate the risk factors[34].

Traumatic injury of periodontium

The forces applied by different ways in the tooth consequently results in the traumatic injury in the periodontium which may or may not lead to displacement of tooth in its socket. Such traumatic dental injuries usually injure teeth as well as the periodontium and inadequate prognosis often leads to tooth loss[35]. The forces leading to traumatic injuries in the periodontium are of three major types which include occlusal forces, orthodontic forces and a physical blow[36]. The occlusal forces depend upon the arrangement of teeth as well as structure of the face while the orthodontic forces depend upon the dental treatment strategy and physical blow to tooth occurs by falls, sports activities, traffic accidents or physical fights[37,38,39,40]. All of these forces tend to cause disruption in the periodontal ligament as well as alveolar bone thus affecting the tooth function as well as has negative impact on esthetic and psychological perspective[41].

Experimental model for periodontal diseases

The severity of the periodontal diseases is the bone destruction which is due to formation and activity of increased number of osteoclasts[42]. Therefore, most of the research works are focussed in preventing bone resorption due to inflammatory reactions during the course of periodontal diseases. Since last several year different models of periodontal disease have been employed to study and prevent the inflammatory bone loss. All those disease models fall either under in vivo or ex vivo models[42,23]. Although Sloan and colleagues in 2013 reported an ex vivo model to study inflammatory bone destruction, in vivo models of periodontal diseases using non-human primates, miniature pigs, Dogs, Ferrets, Rabbits and rodents are used and indeed the rodents are the most common models[43].

There are three different methods to induce periodontal diseases in rodent animal models which include Ligation model, bacterial infection and/or inoculation models and Lipopolysaccharide injection models[44,45,46].

Ligation induced model

The ligature induced periodontal disease model is the most common method of inducing periodontal disease in experimental animals[43]. Mostly silk ligature are placed around the molar which facilitates dental plaque formation and ulceration in the sulcular epithelium resulting in bacterial invasion into the connective tissue thus initiating the periodontal inflammation[45]. The inflammation progresses day by day causing destruction of the surrounding soft tissues as well as alveolar bone as a sign of periodontitis in about 7 days after ligation[47].

Lipopolysaccharide injection model

Lipopolysaccharide (LPS), an endotoxin is a major constituent of the cell wall of Gram-negative bacteria that initiates the host immune response contributing to inflammatory reactions[48,49]. The purified bacterial LPS suspension is injected using thin needles usually into the gingiva of the palatal side of molars[44,50]. Upon injection of LPS, the host innate immune system is initiated releasing inflammatory cytokines that enhances osteoclastogenesis and bone loss which can be observed around 7-10 days after injection[51].

Bacterial infection and/or inoculation models

The major cause of periodontal diseases is the dysbiosis of the bacterial flora of oral cavity[26)]. Therefore in bacterial infection/inoculation model, periodontopathogenic bacterial strains like Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Tannerella forsythia and Treponema denticola are commonly used to initiate infection[52,53,54,55,56,57)]. Bacterial infection/inoculation process is carried out by oral gavage with viscous suspension of 2% carboxymethylcellulose consisting of 109 CFU/ml of bacteria for 1 week[50)]. The animals infected with bacterial inoculum develop periodontal infection resulting in alveolar bone loss usually after 2 weeks of initiating bacterial infection/inoculation[58)]; however the onset of gingivitis may occur within a week.

Future applications using development and disease models

The consequences of periodontal diseases are the disruption of tooth supporting structures which causes loss of tooth function or tooth loss at its advanced state. Therefore, major concern is to prevent the inflammation and retain or regain the functional tooth together with the regeneration of the disrupted tooth supporting structures after the disease conditions. The most common practice is the surgical intervention which is painful, time consuming and expensive so non-surgical approach could be another best alternative for the cure of diseases. Given this, different animal disease models can be employed mimicking human periodontal disease conditions in order to evaluate the efficacy of various therapeutic compounds in healing and regenerating the disrupted periodontal structures. As regeneration recapitulates the developmental process, it can be expedited by modulation of the signaling molecules involved in the differentiation of the periodontal tissues. Till date, most of the disease models are employed in order to examine the process of bone loss during periodontal inflammation and application of therapeutics to heal and suppress the bone loss[59,60,61)]. Nevertheless, few reports presented the gene based therapy in order to regenerate the associated structures[62,63,64)]. Even though the therapeutics are used, those therapeutics also function by modulating the signaling molecules involved in the affected area. In this concern, the research if focussed on the gene therapy by employing disease models would be one of the best approaches to regenerate the tissue. The selection of gene for therapeutic purpose should be carried out by careful examination of the genes involved during embryonic and post-natal developmental stages. As different reports have already disclosed the direct or indirect roles of different signaling molecules in periodontium development, those signaling molecules could be employed in the disease models. Further, the research also should focus on the alternative approaches to regain function of tooth in case of tooth loss. Moreover, after tooth loss, the only alternative approach is the dental implant to regain tooth function which needs well-formed bone in the exfoliated area. For the regeneration of the bone, again the approach of gene therapy, based on knowledge of developmental biology is crucial. Besides these, preparation of scaffolds carrying signaling molecules would be another approach to regenerate the bone and regain the tooth function.

Conclusion

Periodontal diseases pose a major problem of loss of tooth function together with disintegration of the periodontium. Therefore, it has become a major concern for researchers worldwide to develop novel remedial measures in lieu of the common invasive procedures to prevent and overcome the diseases as well as regain the proper structure and function of periodontium. In this concern, besides efficacy testing of therapeutics in different animal disease models, the studies involving the application of signaling molecules from the perspective of developmental biology in order to heal and regenerate the defined periodontal structures should be the main focus of future researches. Particularly, understanding the developmental regulations in periodontium, as a blue print, for proper differentiation and structural formation should be required for proper regeneration and restoration of function.

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한글초록

치주염 극복 및 기능적 재생을 위한 발생생물학기반 치주질환모델

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치아를 지지하는 치아주위 조직은 다양한 치주질환으로 인해 구조 및 기능적으로 문제가 발생하는데, 증상이 심한 경우 치아 자체를 상실 하는 경우도 있다. 치아의 상실은 건강과 삶의 질을 결정하는 중요한 부분으로 작용하기 때문에 치주질환으로 인한 치아상실 및 기능적 문제점을 적극적으로 예방하고 실질적으로 극복할 수 있는 기반 연구결과의 도출이 절실히 필요한 실정이다. 현재까지 다양한 치료방법 및 약물을 이용한 치주조직 재생과 치료에 관한 연구가 진행되고 있는데 이러한 내용을 뒷받침할 수 있는 연구기법 및 최신 연구결과를 본 논문에서 확인하고자 한다. 특히 발생생물학적 관점에서 치주조직의 형성과정 및 이에 관여하는 신호전달체계를 적용하는 방식의 치주조직 재생기법을 확인하고 이와 관련된 다양한 치주질환 실험모델을 확인하고자 한다. 본 논문을 통해 보다 효율적인 치주질환 극복 기술이 개발될 수 있는 계기를 마련하고자 한다.

주제어: 치아주위조직, 실험기법, 치주염, 치은염, 재생