

Role of Animal Model in Periodontal Research

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Abstract: The human periodontium is a uniquely complex vital structure, supporting and anchoring the teeth in their alveolar sockets, thereby playing a decisive role in tooth homeostasis and function. Animal models and cell cultures have contributed new knowledge in biological sciences, including periodontology. Periodontitis is a chronic immunoinflammatory disease initiated by complex subgingival biofilm, containing several putative periodontal pathogens. Although cultured cells can be used to study physiological processes that occur during the pathogenesis of periodontitis, the complex host response fundamentally responsible for this disease cannot be reproduced in vitro. Among the animal kingdom, rodents, rabbits, pigs, dogs, and nonhuman primates have been used to model human periodontitis, each with advantages and disadvantages. Experimental models have been developed in order to reproduce major periodontal diseases (gingivitis, periodontitis), their pathogenesis and to investigate new surgical techniques. Therefore, this review article describes in detail the merits, demerits and application of various animal models and their contribution to periodontal research.

Keywords: Animal model, periodontal disease, gingivitis, Experimental model, periodontal surgery.

INTRODUCTION

Periodontitis is a chronic immunoinflammatory disease initiated by complex subgingival biofilm, containing several putative periodontal pathogens.

In the quest for understanding the etiopathogenesis and treatment outcomes of periodontitis, human cell culture were found to be useful models for replicating some aspects of periodontal disease process of cellular level, however the information about complex host responses was not prominent. In addition, human longitudinal studies pose many problems such as determining individual at risk level of disease activity and susceptibility to disease progression. Hence various animal models are being used to study the pathogenesis of periodontitis to assess therapeutic modalities. Various animal species like non-human primates, rats, dogs, rabbits, pigs, hamster and ferrets are most commonly employed. The smaller animals are generally preferred for research on bacteriology and immune response, whereas large animals like nonhuman primates and dogs are selected for regenerative medicines research due to the reproducibility and surgical accessibility of experimental defects. Therefore, this review article describes in detail the merits, demerits and application of various animal models and their contribution to periodontal research.

Criteria for selection of animal model [1]

- Appropriateness as an analog.
- Transferebility of information
- Genetic uniformity of organisms when applicable.
- Background knowledge of biological properties.
- Cost and availability.
- Ease of and adaptability to experimental manipulation.
- Ecological consequences.
- Ethical implication

However the selection of animal model largely depends on the type of study to be undertaken (i.e. for pathogenesis, immune response, evaluation, regeneration).

Rationale for using animal models in periodontitis

Animal model for testing periodontal regeneration are necessary because controlled qualitative histological analysis is required to evaluate the quality and extent of newly formed supporting tissue. These studies are not possible in man because of periodontium in large blocks for appropriate histological analysis.

- Proper evaluation of new therapy necessarily involves the use of treated and untreated controls which are difficult to obtain in humans.
- The testing of potentially harmful new devices and drugs may be unethical in human prior to thorough evaluation in higher animals
- For the development and research of periodontal vaccine.
- For research in implant therapy and periimplantitis.

Animal models used for pathogenesis of periodontal disease

Various animals are selected based on similarities in physiological and anatomical features of oral cavity and periodontitis as well as presence of causative factors responsible for development of natural periodontal disease.

Anatomy

In nonhuman primates the anatomy of teeth and roots is close to that of human, but size is smaller. Although periodontal tissues and the size of teeth in dogs are quite similar to those observed in humans. However some major differences exists between dogs and human, lack of lateral movements , no Occlusal contacts for all premolars and presence of open contacts between teeth. In rats, there is continues eruption of teeth and results in movement of teeth in Occlusal distal-buccal direction compared to occluso mesial drift in humans. In sheep the incisors have very short routes and are physiologically mobile. In nonhuman primates the histological structure is similar to that of human periodontium. Marked differences in dogs in presence of gingival sulcular and crevicular fluid is seen. The junctional epithelia and epithelial attachment extend to most coronal level of gingival margin. In rats the crevicular epithelium is keratinized, there is desmosomal contact between the most superficial cells of gingival epithelium and non-keratinized cells of junctional epithelium. In hamster, the interdental septum is narrower than the rats.

Microbiology

In macaca fascicularis (cynomolgus monkeys), the composition of plaque is gram positive rods and cocci for supragingival plaque and anaerobic gram negative rods for subgingival rods [2]. In the swamp rice rat, gram positive bacteria like *S. Sanguis*, actinomyces and lactobacilli have been isolated at 5-9 weeks of age from the oral cavity.

Calculus

The domestic ferret as a study model for periodontitis was originally described by King *et al.* [3]. It is the most suitable models for study of calculus because of its resemblance to human calculus and the fact that information of calculus is not diet dependent as in rats and hamster.

Gingivitis and Periodontitis

Certain species of non-human primates like rhesus monkeys, cynomolgus monkeys and baboons are susceptible to naturally occurring periodontal disease [4]. The inflammatory response to periodontal disease is quite similar to that found in human. Connective tissues are infiltrated by plasma cells, lymphocytes and neutrophils. All domestic dogs have natural to have increased severity and prevalence with age faster than in human but with same etiological factors. Gingival recession appears in severe form of periodontitis in dogs. In early gingivitis the inflammation is limited to the marginal gingiva with presence of neutrophils and monocytes leaving most of the tissue free of infiltrate. Preexisting gingivitis progresses to periodontitis with formation of periodontal pockets lined with typical pocket epithelium. The connective tissue is densely infiltrated with plasma cells and lymphocytes. The osteoclastic bone resorption may result in deep narrow lesion extending vertically around a single root leaving the interdental septum intact [5]. The swamp rice rats are highly susceptible to periodontal disease beginning as early as 2 weeks of age. The gingival tissue becomes swollen with pocket formation, accumulation of plaque and calculus and ulceration at about three months of age. In hamster after diet induced plaque accumulation there is breakdown at the junctional epithelium and formation of crater like gingival pocket. Osteoclastic activities are more on palatal and interdental sites than the buccal sites. Due to thin narrow interdental crest, bone loss pattern is usually horizontal Ferrets presents with similar progression and destruction following periodontitis to that seen in humans. Mice naturally develop periodontitis starting at about 9 months of age with further increase in severity with age as in humans. The ranch raised minks carry the chediak higashi syndrome and develop aggressive periodontitis with severe periodontal tissue destruction and bone loss. The marginal gingiva is infiltrated with neutrophils and proliferation of blood vessels, the epithelium extends deep into connective tissue and space occupied by connective tissue decreases dramatically. In minks neutrophils play a key role in periodontal tissue destruction due to deficiencies in chemotactic response and massive release of lysosomal enzymes and proteases in periodontal tissue.

Animal models used for studying effectiveness of periodontal therapy

In last ten years various surgically created periodontal defects have been used to study impact of GTR or GBR and application of biologics like EMD, BMP2, FGF2, TGF β and PDGF. Experimental defects can be obtained in three ways:

- Acute defect model: Defects surgically created
- Chronic defect model: Lesion obtained by placing orthoelastics, silk sutures, or ligatures around teeth during 12-24 weeks.
- Combined acute /chronic defect model: Defects are surgically created and ligatures are placed to ensure

plaque and calculus accumulation and prevent spontaneous regeneration of defects.

Nonhuman Primates

A variety of defect configuration has been surgically created in non-human primates like palatal dehiscence [6], infrabony defects [7], Class II and III Furcation defects, and fenestration lesion. All these defects have been tested for regenerative therapy using "New medical formulated materials" (NMF). However, a combined acute/chronic defect model is better (by placing cotton floss ligatures or ortho band in defects) as it allows for greater observation, window for regenerative response to NMF, also the chronic defect closely resemble those in human situation with respect to microbial flora and inflammatory reaction.

Dogs

More than 100 Research papers were found in periodontal research involving dogs for healing defects with various membrane, bone grafts and biomaterials. Apart from Furcation and infrabony defects, dogs have served as suitable animal model in mucogingival surgery by creating recession on canine were treated either by palatal connective tissue grafts or GTR with or without biomaterial [8]. More recently, a study in dogs has reported research on mesenchymal stem cells and tissue engineering in treatment of periodontal disease[9].

Rats

Cementum and bone regeneration has been evaluated following delivery of BMPs[10].

Application of animal models for studying periimplantitis and its management

Mombelli and Lang [11] were first to report on the interaction of microbiological flora and implant failure. Since then various investigators have examined the microbiological status associated with implant failure. GBR techniques have been successfully applied in treatment of periimplant bone defects in dogs and monkeys. Furthermore rabbits have been mainly used for testing biomaterials and their effectiveness in periimplant defects. Schou *et al.* [12] evaluated effectiveness of autologous bone graft particle in combination with ePTFE membrane in treatment of periimplantitis in 8 cynomolgus monkeys. Schwartz *et al.* [13] stated impact of rh BMP2 with bone block or implantoplasty for ligature induced periimplantitis in beagle dogs.

Animal Model Used for Developing Periodontal vaccine

Vaccine trials in animal models are required for safety and efficacy testing of vaccines. The ideal animal research model for vaccine trials against periodontitis with naturally occurring periodontitis based on same etiology, pathogenesis and prevalence in animals as well as human doesn't exist. As substitute

experimentally induced periodontitis models have been used. Animals such as mice, rats, hamsters are useful in testing immune response and for safe studies. Also nonhuman primates like *M.Fascicularis*, *M. Nemestrina*, and Baboons have been considered for periodontal vaccine trials. Sheep have naturally occurring periodontitis as *P.gingivalis* strains found in them are homologous to human *P. gingivalis*, also there is similarity in humoral immune response and hence suitable for vaccine trials.

Limitation

- Not all human disease can be reproduced in animals.
- The entire conclusion derived from animal experiments may not be strictly applicable to human beings.
- Ethical consideration.
- Difficulty in breeding and maintaining certain species of animals.

CONCLUSION

Experimental models for periodontal diseases are essential for understanding the origin and evolution of the pathology in humans. The use of animal models in periodontal research is a necessary step prior to entering into clinical trials with new biomaterials and treatments. New avenues are now available in periodontal research, allowing larger cohorts that are easier to maintain. A more systematic use of these small animal models appears evident for future research, especially from a surgical point of view.

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